Project Final Report

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List of Abbreviations/Acronyms

ADM	Admission
APOE	Apolipoprotein E
aPTT	Activated Partial Thromboplastin Time
CANTAB	Cambridge Neuropsychological Test Automated Battery
CC	Corpus Callosum
CDE	Common Data Elements
CENTER-TBI	Comparative European Neurotrauma Effectiveness Research - TBI
CER	Comparative Effectiveness Research
CINTER-TBI	Collaborative Indian NeuroTrauma Effectiveness Research
CNN	Convolutional Neural Networks
CRASH	Corticosteroid Randomisation After Significant Head Injury
CRF	Case report form
CT	Computerized Tomography
DAI	Diffuse Axonal Injury
DALYs	Disability-adjusted life years
DCTF	Data Curation Task Force
DNA	Desoxyribo Nucleic Acid
DoW	Description of Work
DTI	Diffusion Tensor Imaging
DVT	Deep Vein Thrombosis
ED	Emergency Department
EEG	Electro encephalogram
ER	Emergency Room
EVD	External Ventricular Drain
FA	Fractional Anisotropy
FTE	Full time Equivalent
GAIN	Genetic Associations in Neurotrauma
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
GOSE	Glasgow Outcome Scale Extended
GUPI	Global Unique Patient Identifier
HR	High Resolution

HRQoL	Health-related quality of life
ICD-9/10	International Classification of Diseases 9/10
ICM+	Neuro-Intensive Care Monitoring system
ICON	Clinical Research Organization
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IMPACT	International Mission for Prognosis and Analysis for Clinical Trials in TBI
INR	International Normalized Ratio
InTBIR	International Initiative on TBI Research
IRB	Institutional Review Board
IQR	Interquartile Range
IRB	Institutional Review Board
ISS	Injury Severity Score
LMIC	Low and Middle-income Countries
LSR's	Living Systematic Reviews
MC	Management Committee
MD	Mean Diffusivity
MLS	Midline Shift
MLT	Machine Learning Technique
MMT	Medical Mobile Team
MR(I)	Magnetic Resonance (Imaging)
MOR	Median Odds ratio
mTBI	Mild traumatic Brain Injury
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
OR	Odds Ratio
PCS	Post Concussion Symptoms
PTSD	Post-Traumatic Stress Disorder
QALYs	Quality-adjusted life years
Qolibri	Quality of Life after Brain Injury
Qolibri-OS	Quality of Life after Brain Injury – Overall Scale
RCT	Randomized Controlled Trial
RPQ	Rivermead Post-Concussion Symptom Questionnaire

SaO2	Arterial Oxygen Saturation
SDV	Source Data Verification
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
TAI	Traumatic Axonal Injury
TBI	Traumatic Brain Injury
OM	One Mind
PP	Provider Profiling
VAS	Visual Analogue Scale
VS	Vegetative State
WP	Work Package
YLD	Years Lived With Disability

1 Final publishable summary report

1.1 Executive summary

Traumatic Brain Injury (TBI) inflicts great personal suffering on victims and families, and leads to huge direct and indirect societal costs. Worldwide TBI affects 50 million people, results in substantial disability, and costs the global economy €325 billion annually (corresponding to about one in every €150 of annual global output). In the European Union and the UK approximately 2.5 million people suffer a TBI each year, of whom 1.5 million are admitted to hospital and 57,000 die. TBI is a complex disease, management of which has not advanced for many decades. Clinical care is not underpinned by strong evidence, and is not individualised. However, emerging diagnostic approaches, research methodologies, and the availability of robust risk adjustment models, could improve matching of patients to therapies (**Precision Medicine**), comparison of common treatments (through **Comparative Effectiveness Research; CER**), and more accurate prognostication (of huge value to patients, families, and clinicians).

CENTER-TBI is a large-scale project, aiming to (1) improve characterization of TBI in order to facilitate individualized treatments and (2) identify the most effective clinical care, providing high quality evidence in support of treatment recommendations and guidelines. Leading experts from 47 scientific institutes, worldwide, have worked to generate new knowledge that could improve patient outcomes and reduce the global burden of TBI. CENTER-TBI includes a prospective observational Core Study and a Registry, supported by extensive profiling of participating centres to inform CER analysis. **The Core Study** collected granular data from over 4500 patients in Europe and Israel and an additional 1200 in Australia and India. Enrolment was in three strata, differentiated by care path: (1) patients discharged home from the emergency room (ER stratum); (2) patients admitted to hospital, but not to the intensive care unit (admission stratum); (3) patients admitted to the Intensive Care Unit (ICU stratum). **The Registry** collected basic data on all patients presenting with TBI, aiming to assess representativeness of the Core Study and to analyse effects of structural parameters (e.g. organisational) in greater numbers (recruitment: 22,772 patients). CENTER-TBI is part of the International Initiative on TBI Research (**InTBIR** - http://intbir.nih.gov/).

The Core Study combined emerging techniques (e.g. biomarkers, advanced Magnetic Resonance (MR) imaging, genomics), with innovative approaches to analysis. **It created the largest Imaging repositories and Biobank for TBI in the world**. We have mapped clinical care (and its variations across participating centres) to outcome after TBI in Europe, and identified disparities in care and substantial variation in management. Outcome variations were, however, lower than in previous studies, suggesting improvements in overall care and systems of care. **Best practices** were identified, including the demonstration that routine thromboprophylaxis and avoidance of fluid overload in the ICU were associated with better outcomes, and illustrate that strong inferences about key aspects of care can be made. **Novel insights** were generated regarding multiple aspects of neurotrauma biology, management, and outcome. Examples include: recognition of increasing incidence and poor outcomes of “low impact” TBI in older people who fall; data on the heritability of outcome from TBI; assessment of the incremental benefit of biomarkers and advanced neuroimaging in mapping diagnosis and clinical course; careful analysis of high resolution ICU data to better understand intracranial physiology in intracranial hypertension; recognition that up to 50% of patients with “so called” mild TBI do not experience a full recovery by six months (speaking to the concerns of “concussion” in sport); parcellation of the influence of patient characteristics and injury severity on such outcomes; and understanding the influence of psychological health and cognitive deficits over the spectrum of TBI outcomes. While all these results are highly relevant, we anticipate that from **a public health perspective,** the greatest benefits can be accrued by **improving the follow-up and treatment of patients after mild TBI**.

Research results are being widely disseminated to patients, health care professionals and policy makers, and have already resulted in over **200 peer-reviewed manuscripts** in the scientific literature. Importantly, though CENTER-TBI officially closed at the end of March 2021 after a project duration of 7 1/2 years, our data, imaging, and biosample repositories continue to be open for the scientific business of improving our understanding and management of TBI. These resources, particularly when combined with those in partner InTBIR studies, will continue to deliver outputs that will help to improve patient outcomes in TBI. Ongoing meta-analyses between CENTER-TBI and its sister study in the US,TRACK-TBI, are already providing novel insights and vital confirmation of results. CENTER-TBI and InTBIR have established productive global networks of researchers and research institutions, who will use the **legacy of CENTER- TBI** to improve patient care and injury prevention globally for many years to come.

1.2 A summary description of project context and objectives

Traumatic Brain Injury (TBI) is a major cause of death and disability, causing great personal suffering to victims and relatives as well as huge direct and indirect costs to society. Approximately 2.5 million people in the European Union (EU-28) suffer a TBI, of whom 1.5 million are admitted to hospital and 57,000 die. Worldwide, TBI affects 50 million people and costs the global economy €325 billion annually. This means that one in every €150 annual global output is spent on the costs or consequences of TBI. TBI is a complex disease, but strong evidence in support of treatment recommendations is lacking and clinical management seldom adequately targeted. Conventionally, clinical TBI research has involved reductionist attempts to isolate out single factors for treatment, that do not account for the complexity of TBI and lack generalisability. Modern computational techniques and the availability of robust risk adjustment models facilitate more holistic approaches, such as Comparative Effectiveness Research (CER). CER makes use of differences in treatment and outcome. A specific feature of TBI that favours CER is the large between-centre and between-country differences in management and outcome. CENTER-TBI is a large-scale CER project with the following two overarching **Global Aims:**

(1) To improve characterization and classification of TBI

(2) To identify the most effective clinical care, providing high quality evidence in support of treatment recommendations and guidelines.

The specific aims are:

1. To collect high quality clinical and epidemiological data with repositories for neuro-imaging, DNA, and serum from patients with TBI (WP 1-6).
2. To refine and improve outcome assessment and develop health utility indices for TBI (WP 10, 11).
3. To develop multidimensional approaches to characterisation and prediction of TBI (WP 7, 8, 9, 10, 12, 15).
4. To define patient profiles which predict efficacy of specific interventions ("Precision Medicine") (WP 13, 14).
5. To develop performance indicators for quality assurance and quality improvement in TBI care (WP 13).
6. To validate the common data elements (CDEs) for broader use in international settings, and to develop a user-friendly web based data entry instrument and case report form builder (WP 20, 22).
7. To develop an open source database compatible with FITBIR (WP20).
8. To intensify networking activities and international collaborations in TBI (WP 16, 22).
9. To disseminate study results and management recommendations for TBI to health care professionals, policy makers and consumers, aiming to improve health care for TBI at individual and population levels (WP 18, 19).
10. To develop a "knowledge commons" for TBI, integrating CENTER-TBI outputs into systematic reviews (WP18).

The complexity of TBI and research needs

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 (bruises) or intracerebral hematoma (Figure 1). Structural abnormalities may or may not be visible on imaging. The clinical severity ranges from minor (minimal complaints, no visible structural damage) to unsurvivable. Conventionally, TBI severity is classified according to the Glasgow Coma Scale (GCS: range 3-15) into mild (GCS 13-15), moderate (GCS 9-12) and severe TBI (GCS<=8). Mild TBI is the most common form of TBI, occurring in around 90% of all cases, but has been least frequently studied. So-called "mild TBI" is however not so mild, and long term complaints are not uncommon. 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. Our past work has shown large differences in outcome between centres with up to a six fold higher risk in "poorer" vs. "better" centres after adjustment for chance effects and case mix. Whilst 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, but the evidence underpinning these recommendations is weak. Moreover, current approaches to the characterization of disease severity and outcome have been unidimensional and not undergone refinement for more than three decades. 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 enunciated by the US National Academy of Science. Such improved characterization and stratification allow for more targeted therapies.

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 post-acute settings, and by research that focuses on isolated disease mechanisms and tests highly specific neuroprotective agents in underpowered clinical trials. Indeed, improvements in TBI care have come not from clinical trials, but rather from observational studies, expert guideline development and meta-analysis of individual patient data. However, the large scale international observational studies on TBI in Europe and the USA that underpin these improvements date back at least 20 years, and do not reflect current clinical care. Rigorously conducted observational studies in large and diverse populations have the potential to better characterize the disease and to reshape future care for patients with TBI. We aimed to address this need through provision of a contemporary observational data set with high quality, prospectively collected highly granular data.

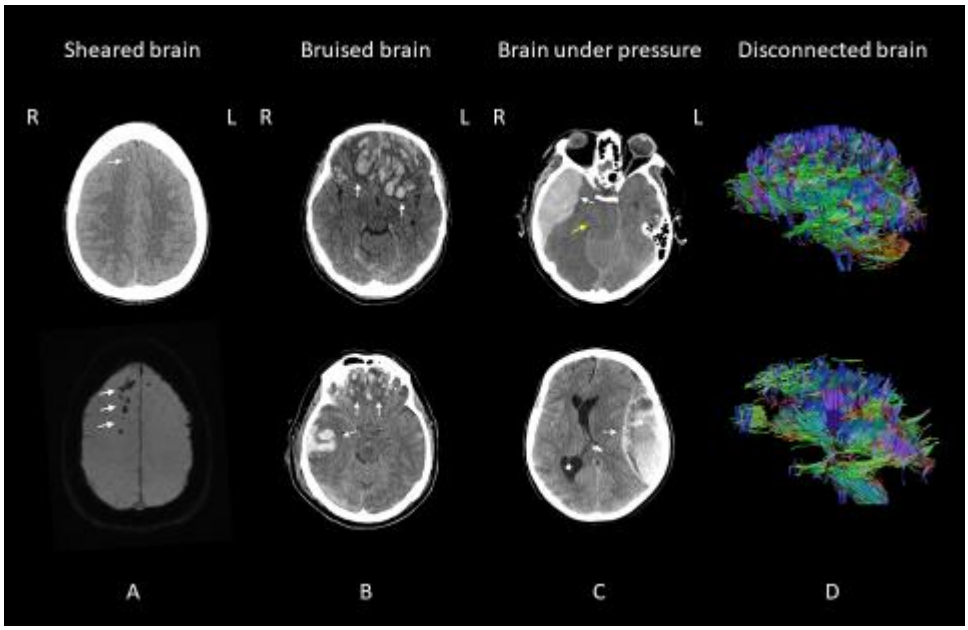


Figure 1: Examples of different types of TBI.

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

CENTER-TBI: Addressing the research needs in TBI

CENTER-TBI brings together leading experts from 47 scientific institutes worldwide. CENTER-TBI is part of the International Initiative on TBI Research (InTBIR - http://intbir.nih.gov/), a collaboration of funding agencies formed in 2011. This initiative provides a platform to encourage international collaborations and application of novel insights and research efforts to improve patient care in TBI. It heralds a shift from the current reductionist approaches to clinical research towards broader approaches requiring multidisciplinary and international collaboration. The basic concept of this project is to **exploit the existing heterogeneity** in biology, care and outcome of TBI patients to discover underlying pathophysiology, to refine characterisation (paving the way for precision medicine approaches), and to identify effective clinical interventions in comparative effectiveness analyses. **Key concepts** of our research plan were to include patients of all severity levels, to follow them along their entire disease course across the chain of trauma care from injury scene to longer-term outcome (Figure 2), and to differentiate analyses by care pathway.

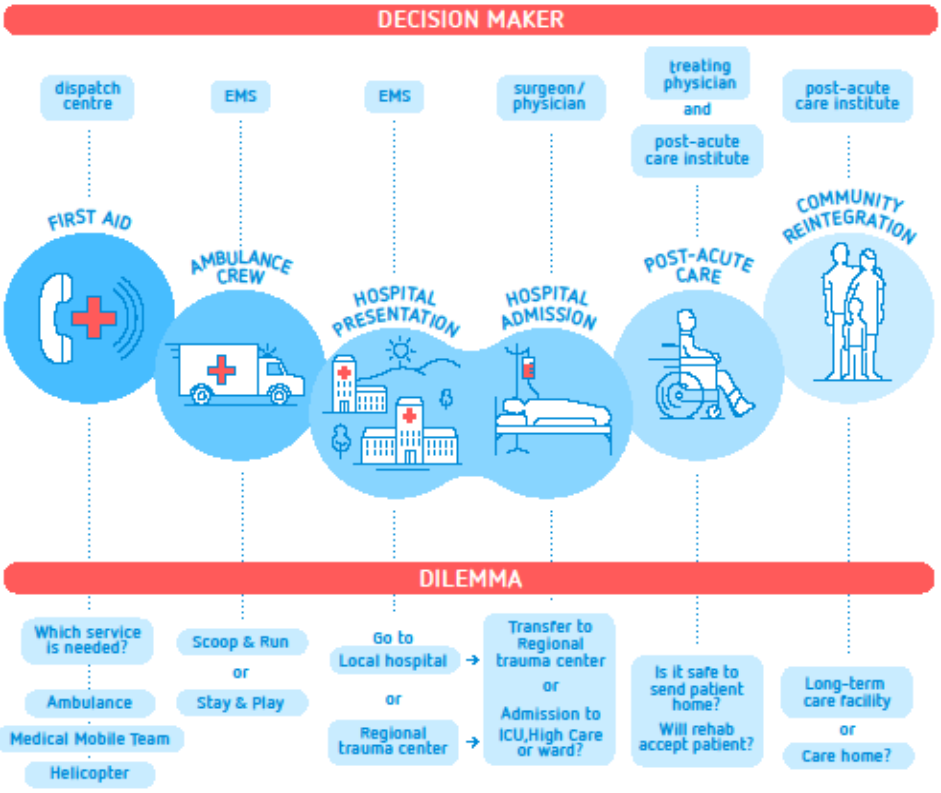


Figure 2: No chain is stronger than its weakest link. Multiple decision points present along the chain of trauma care. Any delays, inappropriate intervention or miscommunication across the links of the trauma chain, incur an increased risk to the patient for complications, poorer recovery or death. EMS: Emergency Medical Service.

CENTER-TBI is an integrative project that optimizes existing knowledge and merges this with new evidence generated from a prospective observational Core Study and a Registry, collecting data on patients with TBI from 20 countries in Europe and Israel. As the study progressed, we have included substantial contributions from Australia, China and India, providing a wider range of clinical practice that allows us to examine greater variations in practice and use such variations to underpin CER analyses. In addition, meta-analysis across studies participating in the InTBIR initiative increases the power of numbers. Extensive profiling of participating centres has been performed to inform CER analysis. In the Core Study, the consortium has collected detailed data in over 4500 patients across all severities of TBI in the EU and Israel and an additional 1,200 in Australia and India. Enrolment was in three strata, differentiated by care path: (1) patients seen in the emergency room and discharged (ER stratum); (2) patients admitted to hospital, but not to the intensive care unit (Admission stratum); (3) patients admitted to the Intensive Care Unit (ICU stratum). Participating centres also maintained a Registry of basic data on all patients presenting with TBI (CENTER-TBI Registry), aiming to assess representativeness of the Core Study and to analyse effects of structural parameters (e.g. organisational) in greater numbers (recruitment: 22,772 patients). The Core Study combines emerging techniques (e.g. biomarkers, advanced Magnetic Resonance (MR) imaging, genomics), with innovative approaches to analysis, including state-of-the-art biostatistics and neuroinformatics. This Precision Medicine approach aimed to allow CENTER-TBI to achieve a step change in the integrated characterization of TBI, and provide clinically relevant constructs that can be used for disease characterisation, pathophysiological inferences, treatment stratification and outcome prognostication. Repositories have been created to allow legacy research with future technologies, benefitting from the extensive and systematic data collection in CENTER-TBI, including long-term outcome. To identify effective medical care (both acute and post-acute), the CENTER-TBI consortium analysed the effects of structure and processes of care at both the organisational (country, region) and at the individual patient level. Treatment of TBI patients varies substantially between centres and countries and depends on trauma organisation, local treatment policies, and physician preferences. In the Quality of Care literature, such characteristics are often differentiated as 'structure parameters' (e.g. level 1 or level 2 trauma centre, patient volume) and 'process parameters' (e.g. choice of surgical procedures, ICP monitoring and management protocols). It is implausible that all of the systems of care or treatment options offer equal benefit: some may well be better than others. However, substantial patient heterogeneity, coupled with relatively small patient numbers (even in larger centres) means that the link between intervention and outcome is

impossible to make in a single centre. CENTER-TBI provides the numbers and methodologies to make such linkages possible. The existing heterogeneity of presentation, differences in management and variability of outcome in TBI provide a compelling argument for rigorous comparative effectiveness research, the outputs of which will provide a rational basis for optimising health care delivery for populations, and clinical management for individual patients.

Research results are integrated with systematic reviews in a process of knowledge transfer and disseminated to patients, health care professionals and policy makers. CENTER-TBI wishes to break with past dogmas and restrictive traditions. As such, the consortium actively seeks global collaborations, includes emergent technologies, involves non-medical scientists, in particular bio-informatics specialists, and seeks collaborative data sharing initiatives. 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 provides novel information on disease processes, treatment, outcome, and prognosis in TBI, identifying new therapeutic targets and therapies; while the CENTER-TBI repositories ensure opportunities for legacy research. Thus, the project has the potential to improve current health care 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.

The project duration was 7 ½ years, including up to 5 years for recruitment and follow-up – revised upwards, due to various delays including those related to COVID-19.

1.3 Description of the main S&T results / foreground

1.3.1 Introduction to structure of this section

CENTER-TBI is a hugely complex project, spanning the entire spectrum of TBI across all severities and along all trajectories of care. The main pillars underpinning our analyses are the **Core study** (with detailed, highly granular data) with its associated repositories (imaging, biomarkers and genetics), and the **Registry**, collecting more basic data in larger numbers. In addition, we included systematic reviews of available evidence, introducing the novel concept of Living Systematic reviews, performed extensive profiling of participating study sites to establish their organisational structures and care preferences, and performed in-depth analysis of (differences in) ethical regulations and physician attitudes with a particular focus on patients with acute mental incapacity (as is common after TBI). Here, we provide an integrated summary of the results obtained and translate these into policy and practice recommendations. We have structured this Report to align with the Specific Objectives of CENTER-TBI (see section 1.2) In the final part of this section, we will summarize findings towards attainment of our Global Aims, and present policy and practice recommendations. Citations listed in blue can be found on the CENTER-TBI website (https://www.center-tbi.eu/), and in section 2.1 of this Report.

1.3.2 Setting the Stage

In preparation for the CENTER-TBI studies – and as part of the CENTER-TBI project - we aimed to present an extensive overview of the current knowledge on TBI epidemiology, treatment and research and to perform a detailed characterisation of the organisational structure and treatment preferences of participating centres to the Core study and registry. A major output was the publication of a Commissioned Issue on TBI for the Lancet Neurology, the leading medical journal in the fields of Neurology and Neurosurgery (Figure 3). The manuscript and associated commentaries are available via the link: http://www.thelancet.com/commissions/traumatic-brain-injury. The manuscript presents an up-to-date and comprehensive overview of the science and practice of TBI and identifies gaps in our knowledge. It is now viewed as the main reference resource on TBI and has already been cited over 700 times. The Lancet Neurology Commission was released at the European Parliament on Nov 7, 2017. The occasion was attended by a patient and his Mother, who made a very compelling plea to put the huge public health burden and needs of patients and their relatives, posed by TBI, high on the political and policy agenda. In addition, the Lancet Neurology published four more conventional reviews on specific topics to supplement the Commission: Coagulopathy (Maegele et al 2017), Targeted treatment in the ICU (Stocchetti et al 2017), Chronic and evolving neurological consequences of TBI (Wilson et al 2017), and Paroxysmal sympathetic hyperactivity after acute brain injury (Meyfroidt et al 2018). The evidence base was expanded by 5 Living systematic reviews (a concept pioneered by CENTER-TBI) and 19 conventional systematic reviews (see section 1.3.12).

Extensive provider profiling of CENTER-TBI centres was performed prior to start of data collection and the outputs of this process were published in 11 manuscripts. Additionally, an abbreviated version of the provider profiling performed in Europe was completed by the 45 Chinese centres that participated in the China Registry data collection. We observed both some concordance and substantial variations regarding various aspects of TBI care between Chinese and European centres There were more dedicated neuro-intensive care units in Chinese centres than in Europe (97.8% versus 59.7%) and treatment decisions in the ICU were mainly determined by neurosurgeons (57.8%) in China, while in Europe (neuro) intensivists often took the lead (61.2%). For treatment of refractory intracranial hypertension, a decompressive craniectomy was more frequently seen as general policy in China compared to Europe (89% vs 44.6%).

Figure 3: Cover of the Lancet Neurology Commission on TBI, produced by CENTER-TBI and international collaborators

Patient quote after TBI: *"Life is like looking at myself in a broken mirror"*

Lancet Neurol. 2017 Dec;16(12):987-1048. doi: 10.1016/S1474-4422(17)30371-X. Epub 2017 Nov 6. PMID: 29122524.

http://www.thelancet.com/commissions/traumatic-brain-injury

IRB approvals and consent procedures

A basic prerequisite for conducting a clinical study is approval by the country/centre specific Institutional Review Boards (IRB), and implementing procedures for obtaining consent according to national and local regulations. The European Union aims to optimize patient protection and efficacy of health-care related research by harmonizing procedures across Member States. CENTER-TBI, with its broad representation of many European countries,

offered a unique opportunity to explore the degree to which such harmonization has been successful. The CENTER-TBI protocol was evaluated in 18 European countries (excluding Israel) by institutional reviews boards (IRBs) of 66 neurotrauma centers. Fourteen IRBs considered CENTER-TBI an observational study, two an interventional study, as the protocol described blood draws and outcome assessments that would not be part of clinical routine. Primary IRB review was conducted centrally in 61% and locally in 39% of countries. Median time till basic approval was 98 (IQR 94-114) days for central review, considered directly applicable to all national centres, and 50 (IQR: 29-102) days for centres only requiring local approval. Basic approval was reached in one (44%), two (33%) or three (23%) review rounds. Additional local IRB approval was required in 55% of the countries with central procedures and increased the time till final approval. Although additional local IRB approval is generally considered more a feasibility check, in practice a full new review was often conducted. The total median duration across centres from submission of the CENTER-TBI protocol until definitive approval was 114 days (IQR 75-224 days) with a range from 1 to 535 days. We conclude that, despite the aim for harmonization, substantial variation remains in IRB procedures across EU Member States, posing challenges to collaborations in research.

Patient informed consent is one of the basic ethical principles in clinical research. A unique feature of research in TBI is that most patients have acute mental incapacity, and cannot provide consent themselves. Several pragmatic alternatives exist, of which proxy consent is most frequently used. However, proxies may be too overwhelmed by emotions to provide a valid consent, and in emergency situations such as severe TBI, there may be insufficient time to consult with proxies, or proxies are unavailable. An option then is to defer consent to a later moment. We found a significant variation in the use of consent procedures between and within EU Member States. Deferred consent was only used in 26% of the neurotrauma centers involved, although considered valid in 82% of the centers and being described as a valid procedure in the EU General Data Protection Regulation and the Clinical Trials Regulation.

Our experience shows that harmonization of informed consent procedures in EU Member States still needs to be improved. Lack of clear directions in European and especially national legislation result in substantial variation in IRB approval of clinical studies, and this may adversely affect the design and conduct of multinational clinical research on TBI, and more in general on all disorders characterized by acute mental incapacity.

1.3.3 Collection of high quality clinical and epidemiological data with repositories for neuro- imaging, DNA, and serum from patients with TBI (WP 1-6).

The CENTER-TBI Core Study and Registry enrolled patients with TBI from Dec 2014 to Dec 2017. Inclusion criteria for the core study were a clinical diagnosis of TBI, presentation <24 hrs after injury, an indication for computerized tomography (CT) scanning, and informed consent obtained according to local and national requirements. Patients were differentiated by care pathway and assigned to the emergency room (ER) stratum (patients discharged from an emergency room), Admission stratum (patients admitted to a hospital ward), or intensive care unit (ICU) stratum (patients admitted to the ICU). The CENTER-TBI Core study was conducted in accordance with all relevant laws of the EU, if directly applicable or of direct effect, and all laws of the country where recruiting sites were located, including, but not limited to, privacy and data protection laws and regulations, the laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the International Council on Harmonisation guideline on Good Clinical Practice (CPMP/ICH/135/95) and the World Medical Association Declaration of Helsinki. The list of sites, ethics committees, approval numbers, and approval dates is available online (https://www.center-tbi.eu/project/ethical-approval). The Registry collected administrative data not requiring consent and covered a site-specific, convenience-based period during the recruitment period of the core study. A total of 65 sites from 20 countries participated (Figure 4). The CENTER-TBI initiative attracted global interest and included substantial contributions from Australia, China and India (Figure 5).

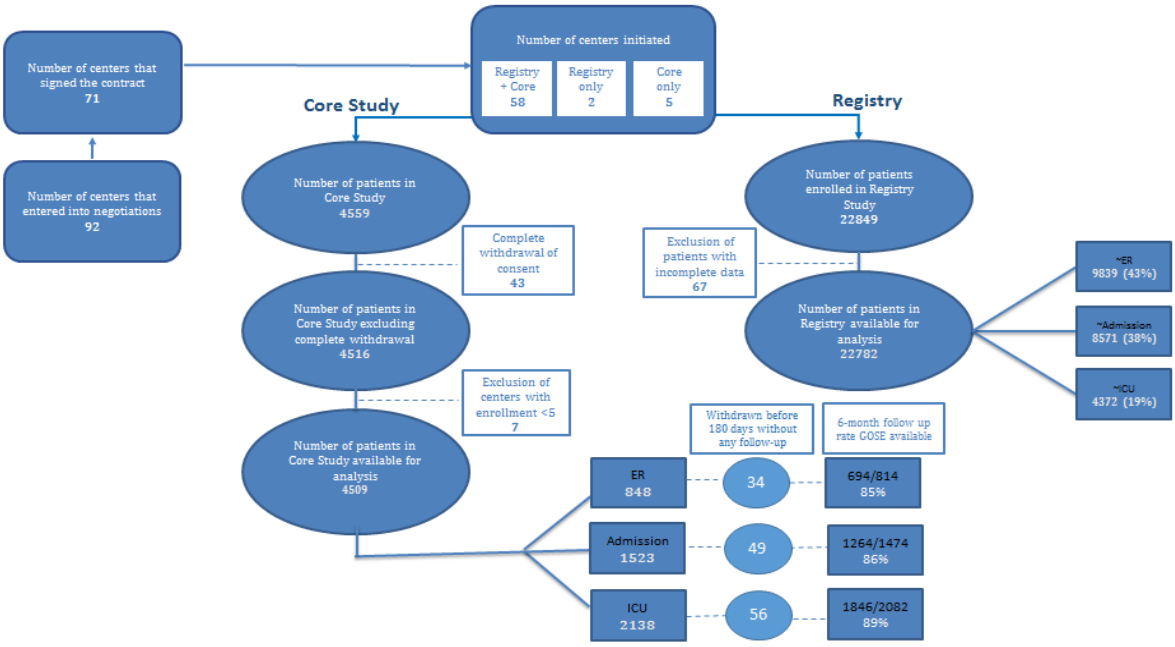


Figure 4: Recruitment to the CENTER-TBI Core study and Registry

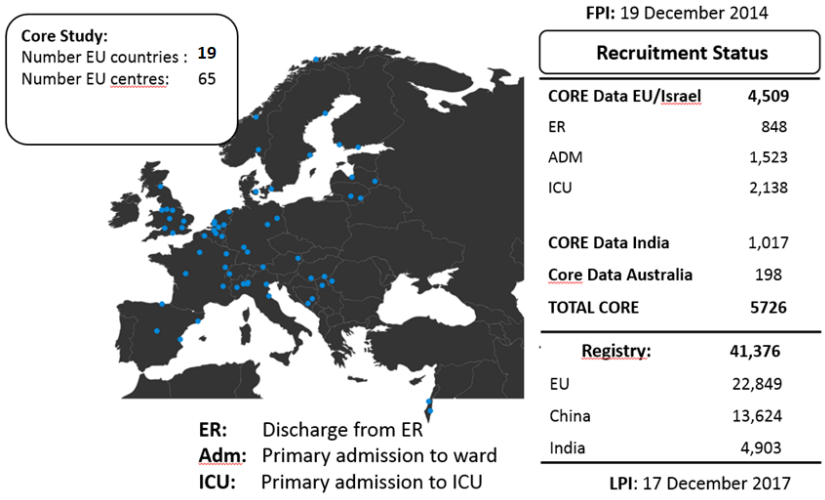


Figure 5: Overall recruitment to CENTER-TBI and CENTER-TBI affiliated studies (OzENTER in Australia, China Registry and CINTER-TBI in India). FPI: First patient In; LPI: Last Patient In.

CENTER-TBI Core Study: Descriptive analysis:

Data from 4509 patients enrolled in Europe and Israel were analysed. Of these, 848 (19%) patients were in the ER stratum, 1523 (34%) in the Admission stratum, and 2138 (47%) in the ICU stratum. The relative distribution across strata to a large extent reflects logistic considerations with regard to enrolment at sites. The strong drive in busy Emergency Rooms for a fast turnover of patients proved challenging for recruiting patients to the ER stratum. A more generalizable picture of care pathways and strata is provided in the Registry. Results of descriptive analyses have been published (Steyerberg et al 2019; Huijben et al 2020). We summarize some of the main findings:

- The median age was 50 years [IQR 30–66], substantially higher than in previous studies, and 1254 [28%] patients were aged >65 years. The high percentage of older patients who suffer TBI is highly relevant as up till now most clinical trials excluded patients over the age of 65. Older patients have therefore been disenfranchised from clinical trials, and as a consequence little evidence exists to support their treatment and guidelines are not applicable to this age group.
- A total of 462 (11%) patients had serious comorbidities, illustrating that TBI is no longer a disease of previously healthy young people. The presence of co-morbidities can adversely affect the disease course.
- A total of 772 (18%) patients were taking anticoagulant or antiplatelet medication. Such medication may lead to rapid progression of haemorrhagic lesions (see also section 1.3.6)
- An incidental fall was the most common cause of injury in the ER (51%) and admission strata (51%), but not in the ICU stratum (41%), where road traffic incidents were the main injury cause (45%).

- Alcohol was contributory in 1054 (25%) patients, but varied by cause of injury (17% in road traffic incidents, 28% in incidental falls, and 64% in violence-related TBI). These data illustrate the success of traffic-related alcohol prevention campaigns, but highlight a need for targeted prevention campaigns to reduce the number of TBIs due to falls, particularly in older people.
- Major extracranial injuries (abbreviated injury score ≥3) were reported in 422 (28%) patients in the admission stratum and in 1174 (55%) in the ICU stratum. The body region most commonly injured was thorax and chest (n=742 [35%]), and concomitant serious spinal injuries occurred in 374 (18%) patients. The co-occurrence of TBI with injuries to other parts of the body emphasizes the need for a multidisciplinary approach to treatment.
- Substantial inter-country differences existed in care pathways and practice, but not in outcome.
- 6 month mortality was 1.3 % (9/694) in the ER stratum, 5.5% in the Admission (70/1264) and 21.3% in the ICU stratum (394/1846). Incomplete recovery (defined as a 6 month GOSE <8) was found in 30% of patients in the ER, 53% in the Admission and in 84% in the ICU stratum. The overall outcome distribution differentiated by stratum is presented in Figure 6. The high percentage of incomplete recovery in the ER and Adm strata, in which most patients had mild TBI, illustrates that "mild TBI is not so mild".
- In patients with moderate to severe TBI mortality was lower than predicted from the IMPACT prognostic model (observed to expected ratio 0.70 [0.62– 0.76]), but unfavourable outcome (defined as a GOSE<5), was not (1.06 [95% CI 0.97– 1.14]). These data suggest that treatment has improved with fewer deaths, but at a cost of more survivors with disability.

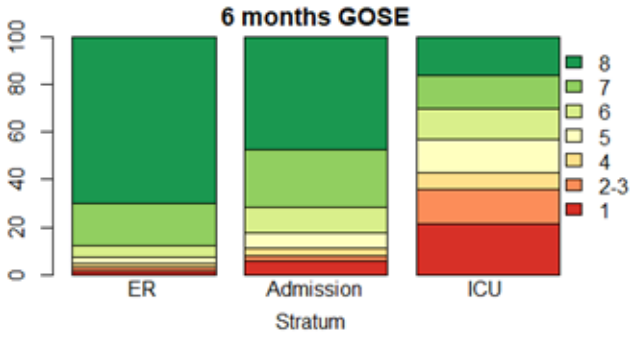


Figure 6: Outcome distribution at 6 months in the CENTER-TBI Core study according to the GOSE, by stratum

CENTER-TBI Registry:

Fifty-six study centres from 17 European Countries and Israel enrolled 22782 patients to the CENTER TBI Registry. A total of 21681 TBI patients - with clinical care pathway and known injury mechanism data - were included for analysis - a median of 247 (IQR 63–473) from each centre. Patients enrolled to the CENTER-TBI registry had a median age of 55 years (IQR 32-75 years), and a 61% male preponderance; 55% had pre-existing medical conditions, 12%(2578) and 11·4%(2466) were taking pre injury anticoagulants or antiplatelet therapy respectively. 82%(17702) presented to the study hospital Emergency Department with mild TBI (Glasgow Coma Scale (GCS) 13-15. Patients presenting directly had CT brain imaging conducted a median of 68 minutes after ER arrival (IQR: 34-141). 31·1% (6746) had abnormalities on CT imaging. The majority (57·1%) were admitted to hospital, 19·2% to intensive care on average two and a half hours after ED arrival. Our analyses focussed on 1) generalizability of Core data and 2) impact of energy transfer mechanisms. Overall, there were differences in patient characteristics between the Core study and the registry, caused by exclusion of patients with pre-existing neurological disorders (including dementia) in the Core study, and differential recruitment to strata with relatively more patients enrolled into the ICU stratum in the Core study. When, analysed by stratum, however, patients in the Core study broadly resembled those in the Registry. These data and comparisons to external registries, such as the UK Trauma Audit and Research Network (TARN), indicate that the CENTER TBI recruiting centres had used an appropriate purposive sampling strategy to recruit patients reflecting the generality of TBI presenting to each centre. Our interest for the impact of energy transfer mechanisms was ignited by the observed high number of older people injured by falls, whilst patients injured by high energy transfer (e.g. road traffic collisions) are prioritised by Emergency Medical Service trauma triage tools as they are considered to have more severe injury. We found that 40% (8622/21,681) of patients in the Registry were injured by low energy falls. These patients have similar rates of CT abnormalities and in-hospital mortality as those injured by other mechanisms, but are 50% less likely to receive ICU care or emergency interventions. This indicates that high-energy injury characteristics should be de-emphasized for injury scene and ED triage of older people with TBI.

CENTER-TBI China Registry:

The CENTER China Registry collected data on patients with TBI admitted to hospitals across China in the same period and according to a similar format as the CENTER-TBI Registry. This intrinsic feature of "twin" studies illustrates the benefits of standardized data collection according to a common format, and highlights the relevance of understanding the heterogeneous nature of TBI and its treatments in different continents. Data of 13138 patients from 52 hospitals in 22 provinces of China were analysed (Gao et al 2020). Most patients were male (9782 [74%]), with a median age of 48 (IQR: 33-61), and 2217 (17%) > 65 years of age. Road traffic incidents were the major cause of TBI (6548 [50%]). Injuries causing TBI most commonly occurred between 9 am and 11 pm and peaked at 10 am (n = 1165; 8.9%). A total of 3882 patients (30%) were transferred from another hospital to the study centre, with substantial variations in secondary referral rates across provinces. ICP monitoring, external ventricular drainage (EVD), craniotomy and decompressive craniectomy were performed in 1509 (11%), 774 (5·9%), 2679 (20%) and 2170 (17%) patients respectively with substantial variation occurring between provinces and centres. Between centre variations were particularly large for ICP monitoring (MOR: 7.64 CI: 4.77-12.98) and for the use of external ventricular drainage (MOR: 9.37 (CI: 4.77 – 18.63). Overall hospital mortality was 4.8% (637), and in severe TBI 19.7% (552). The observed mortality was lower than expected according to the CRASH basic model (O/E ratio 0·49, 95% CI 0·45-0·53). Substantial variation existed between centres (MOR: 2.0 (1.55-2.42)), which is larger than observed in the CENTER-TBI data from Europe. Comparison with the CENTER-TBI data from Europe show that in China, TBI remains a problem primarily of young and middle-aged adults, leading to huge losses in health and labour capacity. We anticipate that the changing demographics (ageing) of the population in China combined with further improvements in road traffic safety will lead to an increase in domestic injuries as cause of TBI in the near future, in particular in older people, thus following a trend observed in high income countries. Between centre differences in treatment and in outcome were larger in China compared to Europe. Whilst the observed differences between provinces and centres offer potential to evaluate the performance of organization and professional behaviour at the level of institutions, they also indicate the need for initiatives to improve health care policy for TBI to take local aspects into consideration and to tailor trauma systems to better fit the situation in different areas. The results of the CENTER China Registry with comparable mortality rates to European data highlight the huge potential that collaborations with China may offer to advance the care for patients with TBI.

CENTER-TBI repositories:

In the context of the Core Study, we have established Repositories for Imaging studies (CT and MR Images), for blood samples and for DNA. These are **the largest in the world in TBI**, offering opportunities for legacy research after the formal end of CENTER-TBI. The Neuro-imaging Repository is maintained by Icometrix (Leuven, Belgium), and contains a total of 8545 CT images, 630 early MR scans and 719 MR scans obtained at follow-up (Table 1). The results of standardized qualitative and quantitative reporting of radiological characteristics have informed many of the analyses of CENTER-TBI.

Table 1: Neuro-imaging Repository of CENTER-TBI

CT		MR acute		MR Follow Up	
Early (at presentation)	4221	Ultra-early (<72hrs)	234	3 months	91
Subacute (in-hospital)	3706 scans 2012 patients	2-3 weeks	396	6 months	262
Postop	618 scans 509 patients			12 months	216
				24 months	150

The CENTER-TBI **Biobank**, maintained in Pecs, Hungary, has been populated with **60187 aliquots from 8026 sample collections of 3803 patients**. Serum samples were divided across 8 aliquots each and stored at -80^{0}C. Three of these aliquots have been used for biomarker assays (S100B and NSE in Pecs and GFAP, UCHL1, total tau and NFL at the McKnight Brain Institute, University of Florida, USA). Collaborations with external academic and commercial Parties have been established to facilitate extended analyses (e.g. metabolomics and lipidomics) and to inform the design of clinical trials. In this context, aliquots have been provided to ABCDx SA; Geneva; Switzerland, University of Örebro; Örebro; Sweden, NanoDx Inc. (former BioDirection); Southborough, MA, USA, and the University of Edinburgh; Edinburgh; UK. A substantial number of aliquots (both pristine and smaller left-over aliquots), however, remain in the Biobank, and are available for novel research initiatives. A total of 3695

whole blood samples were transferred to Cambridge for banking and DNA extraction. Leveraging with samples from previous EU and UK funded studies, we were able to add an additional ~700 samples. After exclusion of patients based on failed DNA extraction, non-European ancestry (so imputation not possible), incomplete outcome data, and missing covariates, genotyping data are available from 3187 patients (73%) for association analysis. Genotyping was performed at the Finnish Institute for Molecular Medicine (FIMM). Aiming for more robust analyses in larger numbers, these data will be combined with a similar exercise in TRACK-TBI (our sister study in the USA) using identical phenotyping and genotyping, and with an additional 409 patients recruited at the Massachusetts General Hospital (Massachusetts General Partners; MGB) in Boston. This has resulted in a total cohort of 4710 TBI patients with European ancestry, and a further 558 non-European ancestry patients –providing a total cohort of 5,268 datasets for genetic association analysis, yielding adequate power to detect OR of ~1.5 for genetic effects in a GWAS. This allowed us to **report the first GWAS/TWAS of TBI outcome**, utilizing **the largest sample** for any genetic association study of TBI to date (see section 1.3.5)

1.3.4 Refining and improving outcome assessment and developing health utility indices for TBI (WP10, 11).

Traumatic Brain Injury should not be considered as “an event”, but as a “process”, resulting in a large number of survivors with with functional, cognitive, emotional and physical consequences. These impairments occur in all grades of severity, and their broad range implies a need for multidimensional approaches to outcome assessment. Conventionally, studies have assessed outcome according to the Glasgow Outcome Scale – Extended (GOSE) that ranges from 1 (death) to 8 (Upper good recovery). In CENTER-TBI, we sought to obtain a comprehensive assessment of outcome, including clinician-reported outcomes, patient-reported outcomes, and performance-based physical and cognitive outcomes. We collected data on functional outcome (GOSE), Health related Quality of Life (generic: SF-36v2, SF-12v2, and disease-specific: Qolibri and Qolibri-OS), anxiety and depression (GAD-7 and PHQ-9), posttraumatic stress disorder symptoms (PCL-5), post-concussion symptoms (RPQ) and cognitive performance (Cambridge Neuropsychological Test Automated Battery (CANTAB), Rey Auditory Verbal Learning Test (RAVLT) and Trail Making Parts A & B). Our main aim was the selection of the most sensitive instruments to inform multidimensional approaches to outcome assessment after TBI, including the refinement of procedures for administration and interpretation of the GOSE, and exploration of inter-dependencies between outcomes.

Linguistic validation and psychometric evaluation

A major challenge was to ensure applicability and comparability of outcome instruments in an international setting. Many of instruments were only available in English or, at best, in a limited number of languages. We undertook linguistic validation and psychometric evaluation. Linguistic validation is challenging as it needs to address semantic, syntactic, cultural and conceptual differences, while maintaining the content of each instrument across languages. In total, 237 translations and 211 linguistic validations were carried out in 20 languages. Psychometric analyses showed that reliability of all instruments was satisfactory to excellent, and that the instruments were comparable with each other and to the original versions. Validity analyses demonstrated that correlations between measures were consistent across languages. Translations of the outcome instruments are **a major output of CENTER-TBI** and provide a solid basis for multinational TBI research and practice. They are available on the CENTER-TBI website (https://www.center-tbi.eu/project/validated-translations-outcome-instruments).

Approaches to GOS/GOSE administration and rating

The GOS(E) is an ordinal scale, that is commonly administered in a structured format, addressing 7 areas of functioning. It may be administered by personal interview, telephone interview or by postal or web-based questionnaire. Assignment of the most appropriate rating (1-8) can be performed centrally, by an automated algorithm or by the Investigator. We explored agreement between interview- and questionnaire-based assessments. Overall, both methods agreed well. However, some differences were noted: Compared to questionnaires, interviewers recorded more problems with work, fewer limitations in social and leisure activities, and more symptoms. Interviewers also sometimes applied judgement when assigning an overall rating, particularly for cases with potentially unfavourable outcomes. However, associations with prognostic factors and patient reported outcomes were very similar in strength for interviews and questionnaires. The findings support the utility of questionnaires in studies where this form of contact can offer practical advantages over interviews. In CENTER-TBI, central assignment of GOS(E) rating was preferred for a composite GOSE. which combined ratings from interviews and questionnaires.

Discussions with our US colleagues from TRACK-TBI revealed that different approaches to assignment of the GOSE rating exist across the Atlantic. In Europe, the intent is to capture the overall consequences of injury for function, including possible effects of extracranial injuries, whilst in the US, the primary aim has been to capture

TBI-related disability and exclude effects of extracranial injuries. Clearly, this may lead to substantial differences in reported outcome outcomes between studies. Although we recognize that in practice it may be difficult to disentangle effects of systemic injuries from those of brain injury, and that attempting to do so risks introducing an element of subjectivity, both approaches may have merits. We suggest that future studies should differentiate between "GOSE-All" (including polytrauma and any side-effects of an intervention) and GOSE-TBI, in which disability that is clearly *unrelated* to brain injury is discounted. A set of guidelines for use of the GOSE was developed in collaboration with colleagues in TRACK-TBI and thus represents a consensus for Europe and North America. The manual covers administration of the GOSE and common issues that arise; it has been published in an open access format to maximise dissemination (Wilson et al., 2021. https://doi.org/10.1089/neu.2020.7527).

Any study, and in particular studies on TBI, can suffer from loss to follow-up. In general terms, imputation is preferred over a complete case analysis. Previous studies, including most clinical trials, have imputed missing values according to the last observation carried forward (LOCF) approach. This approach, however, insufficiently takes the natural recovery trajectory into consideration. We explored alternative approaches to imputation that take multiple time points into account. We found a multi-state model to interpolate missing outcomes based on available observations, both before and after the pre-defined time window for assessment, to function best with performance superior to the LOCF approach (Kunzmann et al 2019).

Outcomes after TBI

Wide-ranging analyses have been performed on the data available (Table 2). At 6 months a GOSE rating was available for 84% of patients, and for survivors completion rates ranged from 55% to 57% for patient-reported outcomes and from 37% to 46% for cognitive tests.

We conducted extensive methodological analyses to examine the ability of assessments to identify differences after TBI, and compare their relative sensitivities. The GOSE (recovery) displayed the highest ability to capture changes in subgroup analyses over all time points, followed by the QOLIBRI and QOLIBRI-OS (TBI-specific HRQoL) and then by the SF-36v2 and SF-12v2 (generic HRQoL). Psychological outcome measures (anxiety: GAD-7, depression: PHQ-9, posttraumatic stress disorder: PCL-5, and post-concussion symptoms: RPQ), the QOLIBRI and the QOLIBRI-OS as well as the mental component of the SF-12v2 and SF-36v2 were found to differentiate well between individuals with premorbid psychological problems, especially at later time points (i.e., 12 months after TBI). QOLIBRI and QOLIBRI-OS were found to be most sensitive in capturing differences between patient subgroups. The PHQ-9 and then the RPQ are able to distinguish functional recovery states as measured by the GOSE at three time points (3, 6, and 12 months after TBI). The PCL-5 and SF-12v2 mental component score (MCS) appeared more sensitive at 12 months after TBI.

Table 2: Number of observations per outcome instrument at four time points, with percentages of impaired scores in brackets

Instrument	2 weeks	3 months	6 months	12 months
GOSE	1006 (74%)	3150 (71%) /3650 (69%)*	3084 (67%) /3674 (64%)*	2319 (69%)# /3678 (54%)*
GAD-7	635 (19%)	2039 (17%)	2122 (16%)	1416 (16%)
PHQ-9	634 (27%)	2044 (20%)	2125 (18%)	1408 (18%)
PCL-5	632 (12%)	2037(11%)	2116 (9%)	1397 (10%)
RPQ	650 (32%)	2084 (30%)	2170 (29%)	1434 (30%)
QOLIBRI	645 (28%)	2067 (26%)	2128 (25%)	1411 (25%)
QOLIBRI-OS	662 (26%)	2140 (26%)	2171 (23%)	1447 (23%)
SF-36v2/ SF-12v2 PCS	666 (42%)	2222 (37%)	2224 (29%)	1480 (28%)
SF-36v2/ SF-12v2 MCS	666 (28%)	2222 (27%)	2224 (24%)	1480 (26%)

* number of imputed GOSE values at 3, 6, and 12 months, respectively
# Observed values for 12 month outcome are restricted to the Admission and ICU strata. This explains the apparent discrepancy between observed and imputed values.
Selection criteria: individuals over 16 years of age, who filled in the outcome instruments at the respective time points.

Six-month cognitive outcomes were collected in 1554 patients, making this one of the largest studies of cognition after TBI conducted to date. We related cognitive functioning to GOSE scores and found that processing speed is

the domain most strongly related to function in daily life (Wilson et al 2021). Deficits in cognitive performance were particularly evident in patients who were dependent (GOSE 3 or 4) or unable to participate in one or more major life activities (GOSE 5) (Figure 7).

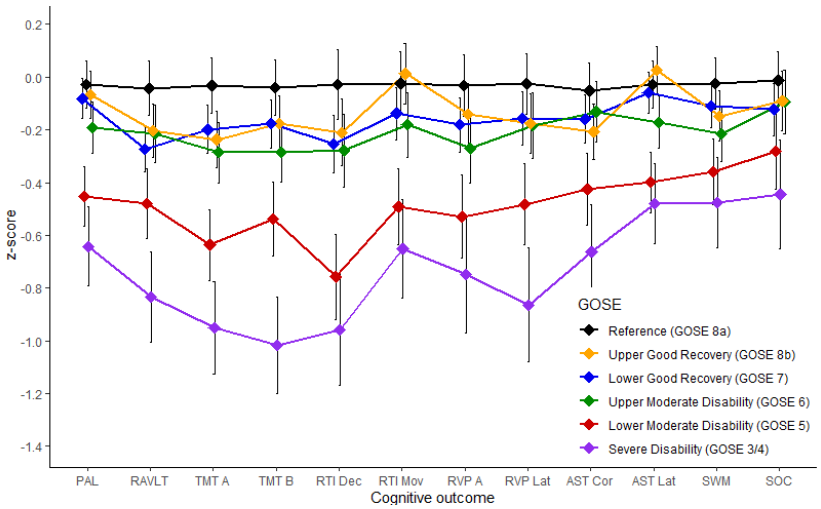


Figure 7: Cognitive function is severely impaired in patients with a GOSE<6, but less so in patients with a GOSE 6-8.

At higher levels of function (GOSE 6 to 8), cognitive performance was similar across categories. We also found that cognitive function was associated with symptoms of post-traumatic stress disorder assessed by the PCL-5. A total of 13% (153/1134) of patients screened positive for probable PTSD. Low performance on cognitive tests assessing attention, cognitive flexibility and verbal long-term memory were associated with probable PTSD following TBI.

A particular focus in our studies was on patients with a mild TBI (GCS 13-15). We found that 50% (1239/2464) had a GOSE below 8 at 6 months, demonstrating that "mild TBI is not so mild". Around 25% had SF12v2 summary scores below threshold for impairment (scores <40) and 26% had RPQ scores ≥ 16, indicating significant postconcussion symptoms. In patients with mild TBI who were discharged home from the ER, the respective rates were 29% (GOSE), 21-23% (SF12v2) and 21% (RPQ).

These high rates of impairments are of particular concern as in current clinical practice most patients discharged from the ER are not routinely scheduled for any follow-up. We explored in greater detail the presence of post-concussion symptoms and other outcomes in patients with complicated (with abnormalities on CT scan) versus uncomplicated (normal CT scan) mild TBI and their evolution between 3 and 6 months. A higher percentage of patients after complicated mTBI were classified as having significant symptoms at three (complicated: 46% vs. uncomplicated: 35%) and six months (complicated: 43% vs. uncomplicated 34%). However, after adjusting for baseline covariates, the difference between complicated and uncomplicated mTBI at three months appeared minimal: odds ratio: 1.28 (95%CI: 0.98 - 1.70). We note that post-concussion symptoms are non-specific and are reported in a substantial proportion of the general population (up to 18% for a rating score of 3, and up to 45% for a rating score of 2). We further note a large similarity in symptoms captured by the RPQ and symptoms reported in long-term COVID, and indeed in other survivors of critical illness. These similarities suggest that some part of the cognitive and psychological features seen in TBI may be a consequence of the host response, rather than the primary injury. Patients after complicated mTBI had significantly lower GOSE scores, and reported lower TBI-specific and generic HRQoL compared to those after uncomplicated mTBI. Both groups showed a tendency to improve from three to six months after TBI. Overall, impairment rates after mTBI were much more strongly related to stratum than to presence of CT abnormalities, suggesting that **selection by stratum** may be more appropriate than targeting complicated mTBI for achieving **an enriched population in clinical trials.** Our data, showing high impairment rates after mTBI, highlight the need to take account of the short and long-term impact on outcome for patients after mTBI, and to provide **structured screening and individualized tailored therapy** when such impairments are detected.

Towards a multidimensional approach to outcome assessment

There is an increasing awareness of the importance of multi-dimensional outcome assessment in TBI, but a lack of practical advice on implementation. We propose that functional outcome can be used as a framework for guiding the application of patient-specific assessments. This is a **'sliding' approach**, which uses severity of disability on

the GOSE as a guide to the suitability of assessments. Support for this approach comes from examining relationships between global functional outcome and other assessments (Table 3) based on cross-sectional data collected from 2573 patients. Outcome completion rates were 80% or above for the entire sample, but substantially lower among patients with severe disability. Impairments of mental health and health-related quality of life were common in all groups except in patients with upper good recovery. Broadly, it appears that assessment might usefully be tailored to at least three levels of recovery (severe disability, moderate disability and lower good recovery) reflecting severity of disability and impairment. Upper good recovery may represent a fourth level, where more sensitive assessments are needed.

Table 3: Summary of findings from CENTER-TBI for assessments of cognition, mental health, and health-related quality of life (HRQoL) at different levels of functional recovery.

GOSE functional outcome	***Cognition***	***Mental health***	***Wellbeing and health-related quality of life***
Lower SD	Up to 73% impaired on individual tests;	Up to 46% report symptoms indicative of depression;	Poor HRQoL in up to 82%;
Upper SD			
Lower MD	Up to 35% impaired on individual tests;	Up to 33% have symptoms of depression;	Poor HRQoL in up to 52%;
Upper MD	Up to 28% impaired on individual tests;		
Lower GR		Symptoms of depression in 17%; ceiling effects on some assessments.	Poor HRQoL in up to 26%;
Upper GR		Symptoms of depression in only 5%; ceiling effects on assessments common.	Poor HRQoL in 11% or less; ceiling effect on QOLIBRI-OS.

Besides a "sliding approach", in the search for multidimensional descriptions of outcome it is logical to consider combining assessments. For example, severe disability can be subdivided based on the extent of impairment. Similarly, upper levels of outcome could be subdivided by the presence of impaired cognition, health-related quality of life, or mental health. For mild TBI, a multidimensional dichotomized outcome can be created contrasting "complete recovery" and "incomplete recovery", in which the latter is defined as GOSE <8 or impairment on another outcome domain. In 2464 patients with mild TBI and complete GOSE assessment, we found that 11% would be rated as having an unfavourable outcome according to the conventional dichotomization of the GOSE (GOS<5 vs GOSE>=5), but that 51% had a GOSE<8. This confirms that dichotomizing the GOSE at a level of <8 versus 8 is more appropriate for mild TBI. We further explored the concept of "incomplete recovery" based on assessment with multiple instruments in a cohort of 1612 patients with mild TBI in whom measures were available. We found that in most cases, a GOSE <8 was the driving impairment (Figure 8).

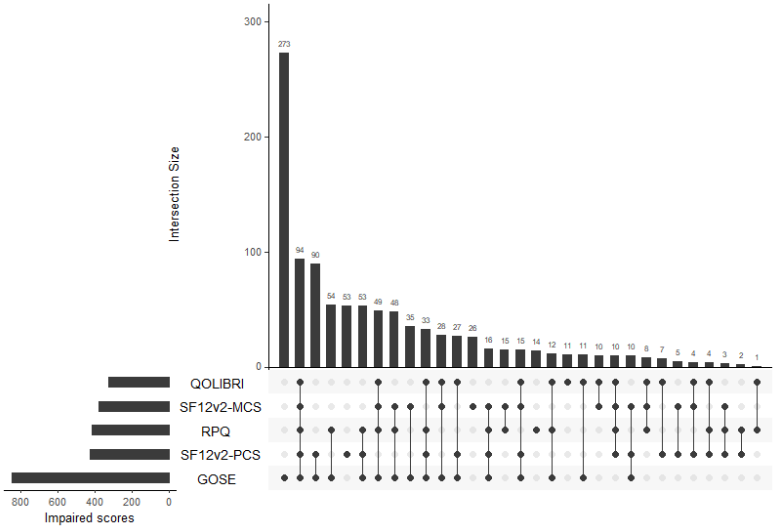


Figure 8: UpSet plot of combinations of impaired scores. Frequencies of impaired scores on individual assessments are indicated by the horizontal bars while combinations of impaired scores are shown by vertical bars.

However, a substantial number of patients had impairments in other domains. Creating a composite outcome, considering in addition to the GOSE, the SF12v2 MCS and PCS, the Qolibri and RPQ scores, we found that 63% of patients would be considered as having incomplete recovery defined by impairment on one or more of the

instruments and 40% when defined by impairments on 2 or more instruments. These approaches comprise **multidimensional outcome tools** that have the potential to better capture the consequences of mild TBI.We suggest that the "sliding approach" is appropriate to clinical practice for targeting additional assessments after TBI and that the concept of **"incomplete recovery"** be considered as **endpoint** for clinical studies on mild TBI.

Health Utility

We performed a web-based survey, which was completed by 13,623 respondents from the Netherlands, United Kingdom and Italy (Voormolen et al, 2020). We derived a value set for the QOLIBRI-OS which allows calculation of utility scores for TBI health states. We also calculated disability weights by Glasgow Outcome Scale Extended (GOSE) severity level derived from health-related quality of life (HRQoL) data of 2215 TBI patients. The utility scores and disability weights are needed for economic evaluations, and for the calculation of summary measures of population health, which may be used to inform decision-makers on the best interventions and strategies for TBI patients. In a case study, we explored this approach to compare the cost-effectiveness of two treatments used to reverse brain swelling after traumatic brain injury: "hypertonic saline" (HTS) and "mannitol" and demonstrated that the statistical power to detect treatments effects is higher when the incremental cost effectiveness ratio (ICER) is based on QALY rather than "good recovery" versus "non-optimal recovery". The development of **disease-specific health utility indices for TBI** now enables **cost-effectiveness analyses** and policy making.

1.3.5 Multidimensional approaches to characterisation and prediction of TBI (WP 7, 8, 9, 10, 12, 15).

Improved characterisation and classification of TBI is essential to developing individualized treatment approaches in the context of Precision Medicine. Although characterisation and classification of TBI are multidimensional concepts, most previous approaches have focused on a single dimension, e.g. clinical severity as measured by the Glasgow Coma Scale (GCS) or the presence of structural damage assessed by computerized tomography (CT scanning), and often reduced these further to over-simplified constructs. Novel approaches (genetic risk stratification, advanced imaging, and emerging biomarkers) could offer substantial gains in Precision Medicine and therapy stratification. Prediction models, which combine several characteristics to predict outcome, have many applications. They can aid precision medicine by identifying patients at higher risk, allowing selection for more aggressive therapies; provide more objective information regarding outcome expectations to patients and their relatives; support timely clinical decision-making; aid stratification of patients in randomized controlled trials (RCTs); and provide a basis for benchmarking quality of care. We present a summary of the CENTER-TBI results in three parts: epidemiological insights, characterization and prediction.

Epidemiological insights

Aiming for an integrated insight into the current epidemiology of TBI, we compared findings from the CENTER-TBI Core study and Registry to those of our living systematic review (for more on LSRs, see section 1.3.12). On comparison between the LSR and Core study, the median ages were very similar (50 and 51 years). The proportion of males was somewhat higher in the systematic review (72% vs 67%). In both cases, falls (46% in CENTER-TBI and 41% in the systematic review) and traffic accidents (38% and 39%) were the predominant causes of injury (Table 4). However, studies in the LSR and the Core Study were biased towards in-hospital patients. The CENTER Registry provides a more general picture of TBI seen in hospitals (including patients discharged from the ER). Here, the higher age and greater incidence of falls as cause of injury were more apparent. We conclude that **TBI is moving towards older ages with incidental falls becoming the predominant cause of injury.** Age is recognised as a strong prognostic factor in TBI outcome, but is associated with comorbidities, treatment of these comorbidities, and frailty (see section 0). Separation of these complex relationships is critical since some aspects (e.g. therapeutic anticoagulation; see later) are correctable causes of poor outcome which demand personalised therapy. Detailed data of the Core Study showed that alcohol abuse was observed in 28% of incidental falls, and in 9% sedatives or sleeping pills were used before the accident. Alcohol-related road accidents were recorded in 17% of cases and abuse of cannabis commonly seen in violence-related injuries (15%).

Table 4: Epidemiological characteristics in CENTER-TBI data compared to LSRs of TBI in Europe

Epidemiological characteristic	Dataset		
	LSR* (update 5, jan 2019	CENTER-TBI Core Study	CENTER-TBI Registry
Patient's age: median (IQR)	51 (27- 45)	50 (30-66)	55 (32-75)
Sex (% male)	72%	67%	61%
Falls (%)	41%	46%	53%
Traffic injuries (%)	39%	38%	26%

* LSR: Living Systematic Review

Characterisation of TBI

In our aim towards innovation, we focused on genetics, (advanced) neuro-imaging, biomarkers and coagulopathy.

Genetic analyses and heritability

We conducted the **first genome-wide and transcriptome-wide association (GWAS/TWAS) study of TBI outcome**, utilizing the largest sample (n=5,268) for any genetic association study of TBI to date. To this purpose, the GAIN consortium (Genetic Associations in Neurotrauma) was established, including patients from TRACK-TBI, previous EU and UK funded studies and a cohort from the Massachusetts General Hospital in Boston (USA). The estimated heritability of TBI outcome was 28 (±14)%. GWAS revealed no hits with genome-wide significance ($p < 5 \times 10^{-8}$), but identified 84 variants in 12 independent loci which met a lower pre-specified sub-genomic statistical threshold ($p < 10^{-5}$) for association with TBI outcome. An exploratory analysis of past published candidate variants only revealed a single variant that reached significance after correction for the number of candidate gene associations studied (rs1800450 in the MBL2 gene). Notably, APOE genotype was not significantly associated with outcome – in keeping with the relatively modest effects we demonstrated in our LSR on Apolipoprotein E4 polymorphisms, despite the many past positive studies. These findings indicate the need for extreme caution when interpreting results from previous candidate genetic association studies that have often been underpowered and subject to publication bias. . The overall heritability estimate we found is consistent with the hypothesis that **common genetic variation significantly contributes to inter-individual variability in host response and TBI outcome, a finding which will be refined in subsequent studies.**

Neuro-imaging

We established the **largest neuro-imaging repository in TBI to date**, including 8545 CT images, 630 early MR scans and 719 MR scans obtained at follow-up (see section 0). We developed tools for automated segmentation and lesion detection of CT images (ico**brain tbi:** https://icometrix.com/services/icobrain-tbi and BLAST-CT: http://deepmedic2.doc.ic.ac.uk:8080/). We demonstrated, that compared to the ABC/2 method, automated segmentations are accurate and have a great potential to expedite the interpretation of large numbers of scans. We showed that central reporting of Neuro-images should be preferred over investigator-based assessments in the context of multicentre clinical studies. For harmonisation of advanced MR imaging, we conducted phantom studies and studies on healthy volunteers.

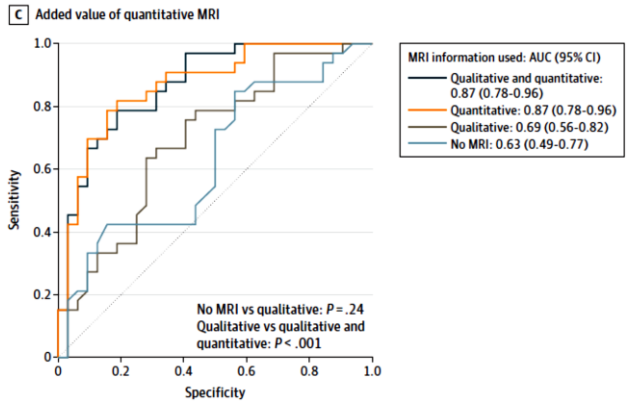


Figure 9: Added value of quantitative MR for predicting outcome after mTBI.

In collaboration with TRACK-TBI we performed a hierarchical clustering analysis of CT features in mild TBI, and identified 3 major clusters of CT features: 1) Contusion/subarachnoid hemorrhage/subdural hematoma; 2) intraventricular, hemorrhage/petechial hemorrhage; and 3) epidural hematoma. In particular Cluster 1 was predictive of both incomplete recovery (Glasgow Outcome Scale-Extended (GOSE) score <8) *and* more severe impairment (GOSE<5) out to 12 months post-mTBI. Our MR studies showed that 30% of patients with mild TBI and a normal CT scan on presentation demonstrated structural abnormalities on MR imaging.

We found that Qualitative MRI added to the prognostic accuracy of outcome prediction beyond conventional clinical and CT based variables, and quantitative volumetric MRI and DTI metrics provided further added value beyond that afforded by clinical reporting of MR images. These findings suggest that advanced MRI reveals potential neuroanatomical substrates of mTBI in white matter and is most strongly associated with odds of recovery if performed within 72 hrs.

The neuroanatomical substrates of persistent late symptoms are particularly difficult to explain in mild TBI, where CT images are often normal, and even structural MRI may show only minimal changes. In this context, we explored functional MRI, and found that individuals with mTBI showed greater global connectivity (p=0.013), yet reduced functional complexity (p=0.027), compared to healthy age-matched controls obtained from the CamCan study (https://www.cam-can.org/). These changes in brain connectivity in mTBI may be a compensatory adaptation to reduced complexity (and hence efficiency) of information transfer.

We further explored the added value of advanced MR imaging in patients with very severe disorders of consciousness after TBI. A model including age and deep white matter diffusion metrics (fractional anisotropy and

mean diffusivity) obtained an AUC of 0.93 on the MRI-COMA training dataset. On the validation dataset, the model successfully (specificity above 95%) identified one in two patients who had an unfavourable outcome at one year post TBI, and two-thirds of the patients who experienced a favourable outcome. These results imply that advanced MR imaging can potentially support decision-making at the individual level within the framework of a multimodal evaluation while the patient is still in the ICU.

Biomarkers

The main focus of our work was on the (added) value of biomarkers for triaging patients with mTBI for CT scanning. We analyzed 6 biomarkers ((S100B, NSE, GFAP, UCHL1, total tau and NFL) in serum samples obtained within 24 hours of injury (2867 patients overall of whom 1951 with mTBI), and related these to the presence of traumatic intracranial abnormalities on the first CT scan (Czeiter et al 2020). All biomarkers scaled with clinical severity and stratum, and with presence of CT abnormalities. GFAP achieved the highest discrimination for predicting CT abnormalities (AUC 0.89 [95%CI: 0.87-0.90]), with a 99% likelihood of better discriminating CT-positive patients than clinical characteristics used in contemporary decision rules. Results were consistent across strata, and injury severity. In patients with mild TBI, GFAP also showed incremental diagnostic value: discrimination increased from 0.84 [95%CI: 0.83-0.86] to 0.89 [95%CI: 0.87-0.90] when GFAP was included. GFAP performed better than S100B, a marker currently included in Scandinavian Guidelines for triaging patients with mild TBI for CT scanning. Combinations of biomarkers did not improve discrimination compared to GFAP alone. We further explored the added value of biomarkers compared to four clinical decision rules ((CCHR=Canadian CT Head Rule; CHIP=CT in Head Injury Patients; NICE= National Institute for Health and Care Excellence; NOC= New Orleans Criteria) in 1889 patients with mTBI. We found that GFAP not only provided added value, but also outperformed all clinical decision rules in diagnostic accuracy. GFAP alone had a higher discriminative ability (AUC) for detecting intracranial abnormalities than the components of the rules, with a relatively small increase when the components of the rule were added to GFAP. **Our results support the development of novel CT decision rules, combining serum GFAP with clinical characteristics, for triaging patients with mild TBI for CT scanning.** Further validation studies are required to determine if GFAP may even replace existing CDRs.

In a collaboration with Orebro University, we undertook a comprehensive metabolomics study, and **the first substantive lipidomic analysis,** in a cohort of 716 TBI patients and 229 non-TBI controls (orthopaedic, internal medicine, and neurological patients). We identified metabolites specifically associated with TBI severity and outcomes. Choline phospholipids (lysophosphatidylcholines, ether phosphatidylcholines and sphingomyelins) were inversely associated with TBI severity and were among the strongest predictors of outcome. These data show that metabolite-based signatures hold promise for improving current clinical or protein-based outcome prediction models. The observed metabolic patterns likely reflect different pathophysiological mechanisms, including protective changes of systemic lipid metabolism aiming to maintain lipid homeostasis in the brain.

Coagulopathy

One in five patients (19.6%) with isolated TBI displayed laboratory signs of coagulopathy based upon conventional coagulation parameters upon emergency department arrival (Böhm et al 2020). Patients on pre-injury anticoagulant and/or antiplatelet therapy had a two-fold exacerbated coagulation profile compared to those without. In patients without pre-injury anticoagulant and/or antiplatelet therapy, conventional coagulation parameters deteriorated with increasing TBI severity. Patients with isolated TBI that were on pre-injury anticoagulant and/or antiplatelet (APAC) therapy had a three-fold higher mortality and a higher frequency of unfavourable outcome at six months (GOSE 1-4) compared to those without (51.9% vs 23.5%). The higher mortality in patients on pre-injury APAC use was confirmed in the CENTER China registry and found to be determined by use of anticoagulants. On more detailed analysis of sequential CT scans (Mathieu et al 2020), we found that lesion progression was significantly higher in the APAC group for extra-axial (3.1 vs. 1.3 mL, p = 0.01), but not intraparenchymal (3.8 vs. 4.6 mL, p = 0.65), intraventricular (0.2 vs. 0.0 mL, p = 0.79), or total intracranial haemorrhage (ICH; 7.0 vs. 6.0 mL, p = 0.08). Extended coagulation profiling in patients with isolated TBI and raised INR displayed deterioration within the thrombin regulating process with increased fibrinolysis and dysregulation of fibrinolysis regulating mechanisms. Increasing endothelial dysfunction (VE-Cadherin) and damage (Syndecan-1, EDMP) indicated presence of endothelial damage in these patients.

Towards a new multidimensional disease classification for TBI

We performed a hierarchical clustering analysis and identified three main characteristics by which TBI can be described: GCS, trauma mechanism, and major extracranial injury (Figure 10) (Gravesteijn et al 2019).

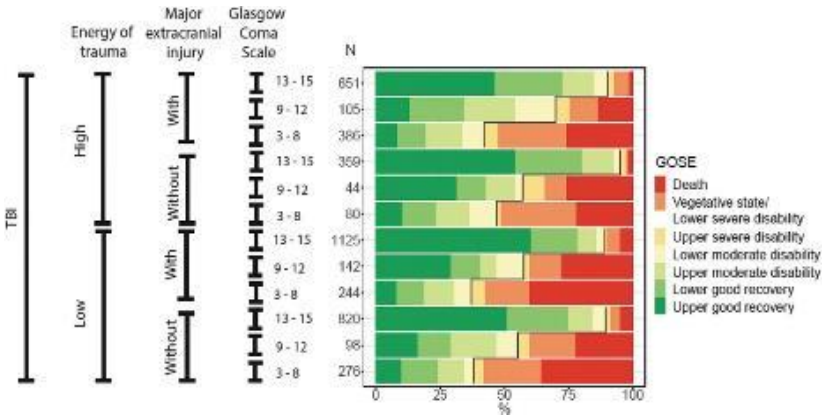


Figure 10: Proposed classification system for traumatic brain injury (TBI) and their observed Glasgow Outcome Scale – Extended (GOS-E) scores.

The classification is based on the characteristics that mostly defined the clustering algorithm. The black line in the stacked bar chart indicates the border of unfavourable and favourable outcome.

Prediction

Many prognostic models exist for moderate and severe TBI (IMPACT[1] and CRASH[2] models), but not for mTBI. None of the existing prognostic models for early prediction of GOSE in mTBI have had both good calibration and discrimination. We externally validated the IMPACT and CRASH models in relevant subcohorts of CENTER-TBI (Dijkland et al 2020). For the IMPACT models, discrimination was good, with AUCs ranging between 0.77-0.85 in 1173 patients and between 0.80-0.88 in the broader CRASH selection (n=1742). For the CRASH models, AUCs ranged between 0.82-0.88 in 1742 patients and between 0.66-0.80 in the stricter IMPACT selection (n=1173). Calibration was only moderate with a lower-than-expected mortality. This indicates a need to update the models. We explored the added value of biomarkers obtained within 24 hours of injury and found that **all biomarkers provided incremental value** with the greatest effect for the combination of UCHL1 with GFAP (increase in AUC from 0.876 to 0.909 for mortality and from 0.850 to 0.876 for unfavourable outcome. We examined the added value of common machine learning (ML) algorithms over logistic regression, LASSO and ridge regression for prediction of outcome after moderate and severe TBI (Gravesteijn, Nieboer et al. 2020). These advanced data analytical techniques did not succeed in better characterization of the complex prognostic patterns in TBI. We further explored prediction of other outcomes than the GOSE in 2666 adult patients who had completed the HRQoL questionnaires at six months after injury. We found that medical and injury related characteristics were of greatest importance for the prediction of PCS, whereas patient related characteristics were more important for MCS and the QOLIBRI following TBI. However, the proportion of variance explained (R^2) was relatively low (19% for the physical component score of SF12, 9% for mental component score and 13% for the QOLIBRI). This could be improved substantially in mTBI by including HRQoL assessments at 2 to 3 weeks after injury. This increased the R^2 to 37% for the PCS, to 36%, for the MCS and to 48% for Qolibri). For patients with mTBI, we developed a new model for early prediction of ordinal GOSE (1-8) based on readily available admission characteristics. The core clinical model included age, sex, psychiatric history, preinjury health, Glasgow Coma Score, and Injury Severity Score. The model had an AUC of 0.70 after correcting for optimism.

1.3.6 Patient profiles which predict efficacy of specific interventions (WP 13, 14)

In this section we consider patient profiles by care pathway, gender effects, disparities in care, efficacy of specific interventions and complications with a focus on comparative effectiveness research (CER) in the ICU population. 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. A basic concept of CER is to study differences in care and outcome in observational studies, thus turning natural variability into an asset. Natural links exist between CER and individualized approaches, as CER aims to identify the best treatment for an individual patient, with a specific type of injury, severity, comorbidities and other aspects that determine optimal treatment.

Patient profiles by care pathway

A unique feature of CENTER-TBI was the differentiation of patients by stratum according to care pathway (ER, Admission and ICU). Overall, 28% of patients in the Core study were over 65 years of age, but this was significantly higher in the Admission stratum (32%) compared to the ER and ICU strata (25 and 26% respectively). This high percentage of older patients with TBI has direct implications for clinical care and research. Most clinical trials to date have excluded patients over 65, and as a consequence evidence to underpin treatment for TBI in older patients is lacking. **A clear need exists for research in older patients with TBI.** Patients in the ICU stratum were more often injured in traffic accidents (45%) compared to the ER and ICU strata (32 and 33%), whilst falls were the most common cause of injury in the ER (51%) and Adm strata (51%). We explored changing care pathways and between centre practice variations in a total of 2138 patients admitted to the ICU in Europe, and found that 36% of patients

were classified as having a mild TBI (Glasgow Coma Scale; GCS 13–15). Some of these admissions are motivated by the presence of serious extracranial injuries, significant comorbidities (especially in older patients), by secondary deterioration, or by a substantial risk of deterioration due to possible progression of traumatic intracranial lesions. However, it appears that some ICU admissions in some centres may be driven by lack of resources on other wards, or by local clinical culture. **Addressing these drivers of inappropriate ICU admission could result in more efficient use of ICU resources.** We noted substantial between-centre variations in the use of intracranial pressure (ICP) monitoring and aggressive treatments (Huijben et al 2020), with Median Odds Ratios (MOR) of 2.5 – 2.9 respectively, but these did not translate into differences in 6-month outcome (MOR: 1.2). This variation in outcome between centres was much lower than observed in previous studies, and posed challenges to CER analyses of specific interventions. However, this observation provides important evidence that **treatment standards have improved over time** - consistent with the lower than expected mortality described in section 0. It further implies that high quality intensive care is likely more important than specific treatment approaches.

Gender, age, and comorbidities – interacting effects

Our data disprove the traditional perception that TBI is a disease of young, otherwise healthy adult males. Our patients were older and commonly had comorbidities (11% with severe systemic disease and a further 32% with mild systemic disease). While male preponderance persisted (67% overall; 73% in the ICU stratum), this was less than in previous studies, and was lost in patients over the age of 75 years. Debate exists if outcome may differ by gender. We explored sex and gender differences in care pathways, treatment characteristics and functional, health-related quality of life and mental health outcomes after mild, moderate and severe TBI (Mikolić et al 2021). We included 2862 adults (36% women) with mild TBI and 1333 adults (26% women) with moderate/severe TBI. We found no substantial differences between men and women in treatment characteristics and care pathways, but **women with mild TBI had poorer 6-month outcomes** across different domains of functioning. Following mTBI, Women under age 45 and above age 65 years showed worse 6-month outcomes compared to men of the same age. We used natural effects models to decompose the total effect of sex/gender on outcomes into indirect effects that passed through the specified mediators (socio-demographic variables and injury-related characteristics) and residual direct effects. We found that outcome differences were not clearly mediated by sociodemographic variables or by care pathways. We conclude that other features underlie observed sex differences in outcomes after mTBI.

Disparities and deficiencies in care

An earlier section detailed the disenfranchisement of patients over 65 years of age in past clinical trials, and our data show significant disparities of care in older patients: In the CENTER-TBI Registry we found that 40% of patients with TBI are injured by low energy falls and these mostly occur in older patients. These patients have similar rates of CT brain scan abnormalities and in-hospital mortality as those injured by other mechanisms, but are 50% less likely to receive critical care or emergency interventions. This indicates that **high energy transfer should no longer dominate injury scene and emergency department TBI triage of injured older people**. Our provider profiling survey on end-of-life practices further showed that age was reported to influence the decision-making process in 81% of the centres (van Veen et al 2020). However, in the Baltic States and Eastern Europe, age did not play a role in 60%, and 50% of the centres respectively. Although strong evidence exists that outcome is poorer with increasing age, **we caution against the dangers of self-fulfilling prophecies.**

We found further evidence for deficiencies in care with regard to discharge policy from the ER and rehabilitation needs. Our provider profiling data showed that 90% of centres do not routinely schedule a follow-up appointment for TBI patients discharged home from the ED, and around 50% on discharge from the ward (Foks et al 2017). In the Core data we found that only 26% of patients discharged from the ER received written information and 6% a follow-up appointment in hospital. Yet, we find that 30% of patients discharged from the ER do not attain a full recovery by 6 months. This indicates **a need for more stringent follow-up and support after mild TBI**.

Clinical outcome at 6 months was classified as moderate to severe disability in1206 of the individuals recruited to CENTER-TBI. Of these, 90% reported rehabilitation needs (Andelic et al 2021), but only 30% received in-patient rehabilitation and 15% out-patient rehabilitation. Physiotherapy was the most frequently provided modality, but cognitive therapy and psychological counselling were provided in only approximately one third of patients reporting impairments in these domains and who may have benefited. These results were confirmed on analysis across the entire CENTER-TBI cohort, showing that in the year following TBI, only 31.4% of patients received rehabilitation services. Significant negative predictors for receipt of rehabilitation were preinjury unemployment (OR = 0.80), living in Central or Eastern Europe (OR = 0.42), admission to hospital ward (OR = 0.47; reference: admission to intensive care unit), or direct discharge from emergency room (OR = 0.24). We conclude that rehabilitation referral is not only driven by clinical needs, but also by demographic and organizational factors, raising issues related to **inequality**

in access to appropriate rehabilitation care throughout Europe. Based on these findings, there is an urgent need to implement national and international guidelines and strategies for access to rehabilitation after TBI.

Efficacy of specific interventions

Airway management: Intubation and tracheostomy

We explored the use and benefits of intubation and of performing an early tracheostomy in ventilated patients (Gravesteijn et al 2020; Robba et al 2020). Intubation was performed in 890/3736 (24%) patients at the accident scene and in a further 460/2930 (16%) on arrival to hospital in the ED. Substantial variation in intubation practices existed between countries (Figure 11). Overall, prehospital intubation had no adjusted overall effect on functional outcome (OR:1.01, Figure 11: Intubation practice variation between countries 95%CI:0.79–1.28, p=0.96), but prehospital intubation was associated with better functional outcome in patients with higher AIS scores in thorax and abdominal (p=0.009, and p=0.02, respectively).

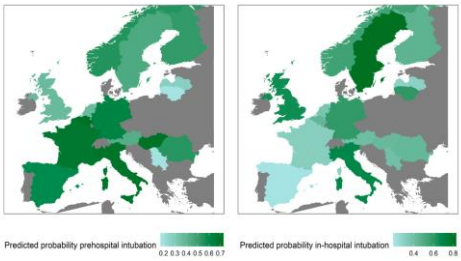


Figure 11: Intubation practice variation between countries

In-hospital intubation showed a non-significant beneficial effect on outcome (OR:0.86, 95%CI:0.65–1.13, p=0.28), but on subgroup analysis of patients with GCS scores of 10 or lower the effect was significant (p=0.01). These results suggest that **major extracranial injury should drive the decision to intubate in prehospital setting**, and that indications for **intubation in-hospital should be broadened to include also patients with a GCS of 9 or 10, rather than ≤8 as is commonly advised.** We explored the benefit of early tracheostomy in patients with an ICU stay >72h and found considerable heterogeneity between countries in tracheostomy frequency (7.9–50.2%) and timing (early: 0-17.6%). Tracheostomy in the first week was associated with a better neurological outcome and reduced length of stay in hospital and ICU. **We need definitive trials to assess the benefit of early tracheostomy suggested by these findings.**

Intracranial pressure monitoring

A total of 921 of the 2138 patients admitted to the ICU (43%) received an ICP monitor. However, 370 out of the 961 severe TBI patients (38.5%) who met authoritative Guideline criteria for ICP monitoring (eg GCS <=8) did not receive an ICP-monitor. The most common reason reported was absence of radiological signs of a raised intracranial pressure. Although guideline adherence for ICP monitoring in patients with severe TBI was suboptimal (61.5%), we found that ICP monitoring had been conducted in 148/328 patients (45%) with moderate TBI and in 12 % of patients with mild TBI. Of all patients monitored, 14.2% were initially classified as mild TBI and 17.2% as moderate TBI. We found substantial between-center variation in ICP monitoring use (MOR: 2.5), duration of ICP monitoring (MOR: 3.2) and guideline adherence (MOR:2.5) (Huijben et al 2020). **We conclude that clinical practice of ICP monitoring use in Europe is highly variable, and deviates from international Guidelines**.

Physiological ICU data with high temporal resolution were obtained from 277 patients and provided important insights on the outcome impact of intracranial hypertension (Åkerlund et al 2020). While BTF Guidelines identify a single ICP threshold of 22 mmHg for treatment, we found that outcome was related to both the intensity and duration of ICP insults, and an ICP threshold threshold of 18 ± 4 mmHg, if maintained for long periods, was associated with poorer outcomes. This clear relationship between pressure/time dose (PTD) and outcome (mortality and unfavourable outcome - Figure 12) were modulated by cerebrovascular autoregulatory status, with greater vulnerability to ICP insults when cerebral perfusion pressure was below the autoregulation lower limit of. **There is a strong case for exploring individualised ICP thresholds for treatment, quantifying the detrimental pressure-time dose of ICP insults, and integrating autoregulatory status into patient management protocols.**

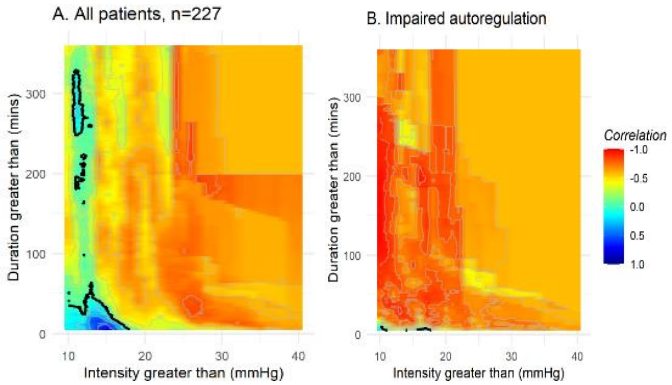


Figure 12: Correlation between number of events above thresholds of intracranial pressure and durations, and outcome (GOS-E). Red indicates that ICP events are correlated to worse outcome at that specific ICP level and event duration on the map. The correlation is lost in impaired autoregulation (PRx > 0.3).

Fluid management

A study of 2125 patients admitted to ICUs in Europe and Australia (Wiegers et al 2021) showed wide between-centre variations in mean daily fluid input (1·5 to 4·2L) and fluid balance (-0.9L to +1.5L). More positive daily mean fluid balance and fluid input were associated with higher mortality and worse functional outcome in both centre-level instrumental variable analysis and patient-level analyses. Each 0.1L increase in daily positive fluid balance was associated with an increased odds ratio (OR) for ICU mortality (range of ORs 1.03 - 1.1) and poor functional outcome (range of OR: 1.04 – 1.09). Higher daily fluid input was also associated with worse outcomes in patient level, but not centre level analyses. We conclude that maintaining neutral fluid balance is not general practice in European and Australian critical care units, and that **Inappropriately high fluid input and positive fluid balance may be iatrogenic (and hence correctable) causes of poor outcome for critically ill TBI patients; addressing this could improve outcomes.**

Deep Venous Thrombosis (DVT) prophylaxis

We analysed data on 2006 adult patients admitted to the ICU and found substantial variation in use of pharmacologic DVT prophylaxis between centres with an MOR of 2.7. A moderate association with better outcome was found at the centre-level (OR: 1.2 [0.7-2.1]), and on propensity matched analysis at the patient-level (OR: 1.4 [1.1-1.7]), which could not be explained by a reduction in number of thrombo-embolic events. **These findings suggest that DVT prophylaxis may be associated with improved 6-month functional outcome and lower mortality rates, without CT progression.**

Surgery for acute subdural haematoma (ASDH)

In an analysis of 1407 patients with ASDH, acute surgery was performed in 336 (24%) patients at a median of 3.8 hours (IQR 2.5-6.5), of whom 245 (73%) received a craniotomy and 91 (27%) additionally a (primary) decompressive craniectomy. The proportion acute surgery varied from 7 to 52% (IQR: 13-35%) between centers. Center preference for an acute surgical strategy compared to that of initial conservative treatment was not significantly associated with better outcome (odds ratio 0.92 [95% CI 0.77 to 1.08]). **We conclude that an aggressive approach to acute surgical evacuation in patients for whom equipoise existed on surgical indication may not lead to a better outcome compared to a strategy favouring initial conservative treatment**

Practice variation in the use of Decompressive craniectomy (DC) and its alignment with evidence

We analysed the harmonised data of the CENTER-TBI and OzENTER-TBI Core studies, which include patients admitted to participating ICUs in Europe the UK and Australia. Patients were compared between different regions and by injury characteristics. Of 2336 people admitted to ICUs following TBI, DC was performed in 320 (13·7%): in 4·5% (64/1422) of patients with diffuse TBI, and 30·5% (195/640) of patients with traumatic mass lesions. Substantial variation was found between regions. Most patients who underwent DC (258/320; 81%) had a primary decompressive craniectomy at the time of evacuation of a mass lesion, and would not have been eligible for either the DECRA or RescueICP trials – the 2 pivotal trials on DC. While current trials (such as the RESCUE-ASDH trial is addressing part of this question, there is currently no evidence to underpin this practice. Consistent with evidence, secondary DC was used infrequently in patients in whom it has been shown to be potentially harmful. However, our data show a **large gap between current practice and available evidence**.

Complications

We found substantial between-centre variation in the occurrence of complications, identified as potential quality indicators (see section 1.3.7): Median odds ratios ranged from 1.5 to 4.1 (Hyperglycaemia: 1.5; Hypoglycaemia:

2.4; decubitus ulcers: 2.5; ventilator-associated pneumonia (VAP): 4.1). We explored VAP, one of the commonest ICU complications, in more detail and found that 1/5 of ventilated patients (196/962) developed VAP at a median interval of 5 days after intubation (Robba et al 2020). Patients who developed VAP were younger, had a higher incidence of alcohol and drug abuse and more episodes of respiratory failure. Therapies as histamine-receptor antagonist intake could increase the risk of VAP, while antibiotic prophylaxis was associated with reduced risk. VAP was not associated with increased mortality or worse neurological outcome but did increase length of ICU stay. **The large between-centre variation in some complication rates indicates substantial room for improving in the quality of care.**

1.3.7 Develop performance indicators for quality assurance and improvement in TBI care (WP 13).

Quality measurement using appropriate indicators can guide quality improvement, for example, through identifying best practices and internal quality improvement initiatives. The potential of quality indicators to improve care has been demonstrated in other clinical areas, in sepsis, in stroke, and in children with TBI. However, quality indicators for general use in TBI are lacking. We explored two approaches to the development of performance indicators for TBI: First, we aimed to develop a set of quality indicators, and second, we explored benchmarking quality of care by comparing observed to predicted outcomes.

We developed a set of quality indicators that have the potential to improve quality of TBI care at European ICU's. This set was developed in an extensive Delphi process, and consisted of 17 structure indicators, 16 process indicators and 9 outcome indicators (Huijben et al, 2019). The indicators were subsequently validated on data from 2006 adult patients enrolled to the ICU stratum of CENTER-TBI in 54 ICU's (Huijben et al 2020). A total of 26 out of the initial 42 indicators could be validated in the CENTER data. The other 16 indicators related to organisational aspects, which could not be evaluated on the patient data of the CENTER core study. Significant between centre variation was found for 7 process and 5 outcome indicators with median odds ratios ranging from 1.51 to 4.14. Statistical uncertainty of outcome indicators was high, mainly due to low event rates. Validity of the indicators was rated according to pre-defined thresholds for feasibility and discriminability. Overall, nine structure and five process indicators showed potential for quality improvement purposes for TBI patients in the ICU. This does, however, not mean that the other indicators may not have value in other settings. Most indicators rated as low potential failed to meet the criteria for discriminability because of high consistence of centres in meeting the indicator standards. This may well be different in settings with fewer resources. The developed indicator set represents **an important tool to support benchmarking and quality improvement programs** for patients with TBI in the future.

Benchmarking quality of care can be based on comparisons between observed and expected outcomes, adjusting for differences in case-mix. Calculating expected risk requires the availability of robust prognostic models. Two robust and extensively validated models for predicting outcome are the CRASH and Impact models. The IMPACT models were validated on 1173 patients with a baseline GCS of 3-12 in the CENTER data and the CRASH model on a broader cohort of patients with a GCS<=14, consistent with the development populations (Dijkland et al 2020). For IMPACT, model discrimination was good, with AUCs ranging between 0.77-0.85 in 1173 patients and between 0.80-0.88 in the broader CRASH selection (n=1742). For CRASH, AUCs ranged between 0.82-0.88 in 1742 patients and between 0.66-0.80 in the stricter IMPACT selection (n=1173). Calibration of both models was moderate. These data support the use of these models for benchmarking quality of care. We further explored observed versus predicted outcome in the CENTER data. In ICU patients with moderate to severe TBI, the rate of unfavourable outcome (GOSE<5) was 55%, similar to that predicted by the IMPACT prognostic model (O/E ratio 1·06 [95% CI 0·97-1·14]), but mortality was lower than expected (O/E ratio 0·70 [95% CI 0·62-0·76]). These findings were recently replicated on analysis of 441 adult patients with moderate or severe TBI, enrolled to our sister study in the US, TRACK-TBI, and show that over time, mortality has decreased but that this comes at a cost of more survivors with severe disability. We note that the IMPACT models were developed on older data, some of which date back to the 1980's. The lower mortality in current practice signals a need for continuous updating of prognostic models. Nevertheless, the potential of **prognostic models for benchmarking quality of care** has been demonstrated.

1.3.8 To validate the common data elements (CDEs) for broader use in international settings, and to develop a user-friendly web based data entry instrument and case report form builder (WP 20, 22).

Standardization and harmonization of data collection in studies on traumatic brain injury (TBI) is of paramount importance to clinical research on TBI, that increasingly involves large scale studies, multicentre international collaborations and data sharing. This requires a "common language" for data collection, in terms of what variables to record and how to code them. The development of uniform data standards – termed "common data elements (CDEs)" – was initiated by the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) study group and taken forward by an international group of 149 institutes and agencies supported, among others,

by the U.S. National Institute of Neurological Disorders and Stroke (NINDS), U.S. Department of Defense, and U.S. Department of Education and the US Department of Veteran's Affairs. This consensus effort lead to Version 1 of the TBI CDEs (TBI-CDE v1), published in 2010. In 2012, a re-structuring was introduced with the overarching aim of creating a set of "Core" CDE elements suitable for use in all TBI studies. "Basic" elements (required for domain-specific studies) were defined according to the following domains: "Concussion/Mild TBI", Acute Hospitalized (AH)", "Moderate/Severe TBI: Rehabilitation (Rehab) and "Epidemiology." A larger set of "Supplemental" elements was created to allow flexibility in adapting to unique study criteria and endpoints. This second version, TBI-CDE v2, is hosted and maintained by the National Institute of Neurological Disease and Stroke (NINDS, https://www.commondataelements.ninds.nih.gov/CDE.aspx). The TBI-CDEs have undergone several updates based on input from expert working groups, researchers and funding agencies. Despite international input, the TBI-CDE's have remained US-centric. We consider the TBI-CDEs of such importance to the field, that they should become global standards. CENTER-TBI provided a prime opportunity to explore the validity of the CDEs in the context of achieving global applicability to support data sharing and international collaboration. In addition, we aimed to quantify the degree of harmonization between three large InTBIR studies: CENTER-TBI, TRACK-TBI and ADAPT. We found an agreement of 81% for CENTER elements with the TBI Core CDEs and 91% for Basic CDEs in the AH domain (Meeuws et al 2020). Non-harmonization was largely caused by absence of the elements in the studies. For elements present, the compatibility of coding with TBI CDEs was 90-99%. The degree of harmonization across the three IntBIR studies ranged from 75% to 87% for the AH domain and for the Rehab domain from 64% to 82%. For each domain the degree of harmonization was greatest between CENTER-TBI and TRACK-TBI. To our knowledge, this was the "first in its kind" study to systematically evaluate the implementation and harmonization of TBI-CDEs across large scale studies. The high degree of harmonization of study variables among these studies demonstrates **the importance and utility of common data elements in TBI research**. This was further re-enforced by the use of these CDEs in or linked studies in Australia (OzENTER), China (China CENTER registry) and India (CINTER-TBI, indicating global interest in their use. A critical appraisal of the TBI-CDEs, however, showed that their presentation on the NIH-NINDS website is not very user-friendly, and identified some major issues concerning global applicability: Some Core elements violate GDPR as they contain potential patient identifiers, e.g., date of birth is a required Core element. Two Core elements (Race and ethnicity) and 2 basic elements (educational level patient and caregiver) are US centric and not applicable to global use. Further, many of the outcome instruments, also those listed as Core elements, are not available outside the English language, or are copyrighted, hence limiting their broad use in international settings. Other issues include duplicates between Core and basic CDEs, overlap between the AH and rehab domains, listing of one variable as multiple elements and discrepancies in classification between domains. These issues have been communicated by e-mail to Dr Mendoza-Puccini, the NINDS lead on the CDE project, and were subsequently presented to the CDE steering committee in March 2020. We understand that work on an update of the TBI-CDEs will be initiated in the fall of 2021, and hope that this may be informed by our critical appraisal and by the empirical experience of the InTBIR studies, including CENTER-TBI. We conclude that, in their current form, the TBI-CDEs do not meet qualifications as global standards. The standardisation of data collection according to the CDEs for TBI is highly relevant to the field and we suggest that **all efforts are made to upgrade these to global standards**, thus facilitating meta-analyses across data collected in different parts of the world. Whilst we can provide input at an individual level, we strongly **suggest formal input** at an institutional level, either **directly from the European Commission or through the InTBIR collaboration**.
Harmonization of data in preparation of meta-analyses, however, goes beyond coding issues. Initial collaborative efforts at meta-analyses between CENTER- and TRACK-TBI have made us recognize that harmonization also needs to address interpretation. For example, we learned that the approach to outcome assignment according to the GOSE was performed differently in the US compared to Europe: In the US, only TBI-related disabilities are considered, whilst in Europe the focus is more on "all-cause" disability (see also 1.3.4). Prior to our work, this substantial discordance had not been recognized, and may well explain why some studies in the US report better outcome compared to Europe. Issues have also been identified with regard to interpretation of coding for pre-injury morbidities and pre-injury alcohol use. **"Deep harmonization"** is required, and substantial efforts will be required in order to perform robust and meaningful meta-analyses. In Section 1.3.9, we describe the analytic platforms developed and implemented in CENTER-TBI. For meta-analyses across studies, we suggest a **"Federated" approach**. Data federation strikes a balance that protects patient privacy and supports clinical discoveries to improve patient outcomes. A federated approach will enable harmonization and analysis of **virtually co-located** studies, while respecting the need for patient data to remain safely behind institutional firewalls. In a cloud-based data federation pipeline, layers of data processing (a.k.a. data virtualization) are introduced between the data user and the primary source data, preventing its direct access. We have explored federated analyses between CENTER-TBI and CREACTIVE in collaboration with the Human Brain Project – MIP to validate prognostic models for TBI.

From a technical perspective, these explorations were highly successful, but perhaps the most important lesson learned was the absolute need for "Deep Harmonisation". Open-source tools and analysis pipelines were designed to incorporate legacy and future TBI datasets, and may be applied to other neurological conditions beyond TBI.

1.3.9 Development of an open source database compatible with FITBIR (WP20).

We aimed to develop, implement and maintain an open standards-based platform for the collection and storage of clinical data and neuroimaging and biomarker results based on Common Data Elements (CDEs). The goal was to develop a next generation open standards-based platform that would support advanced large-scale collaborative analytics and model building, also providing a model for future clinical studies on brain diseases and disorders. The informatics system aimed to (1) provide an open standards based platform where clinical (WP1) and repository (WPs2-6) data would be integrated in a data warehouse, and (2) facilitate collaborative analytics by providing standard interfaces to the platform through which various analytics tools can access the data. The definition of data in the warehouse was designed to be compatible with the FITBIR registry (https://fitbir.nih.gov/). An electronic data collection tool was developed and maintained in partnership with QuesGen Systems Inc. with additional funding from One Mind. All data were de-identified and coded by a Global Unique Patient Identifier (GUPI). Dates and times were rendered untraceable by re-coding all entries relative to UNIX epoch time. Potential identifiers in free text entries were deleted by manual screening and employing an AI algorithm. MR images were defaced upon upload. The CENTER-TBI clinical dataset is extremely complex, including a combination of over 2,400 distinct, discrete and longitudinal measurement concepts with the latter involving both regularly and irregularly sampled timepoints. A bespoke data access tool, Neurobot (details available on the SciCrunch Resource Identification Portal, using the Research Resource Identifier RRID:SCR_017004), was developed, maintained and updated by KI-INCF (Stockholm SE). This was no minor task given the large number of variables, the different types of variables and the inclusion of continuous and longitudinal data. For reference, we initially intended to implement TranSmart[3] (originally developed by Johnson & Johnson with the Recombinant Data Corporation) as our data access platform, but that system failed to cope with the complexity of the CENTER-TBI data. Neurobot provides an easy to use web based front end, which allow investigators "shopping cart-like" access to free text searchable data elements. Within Neurobot, a convenient link is provided to the Data Dictionary, as well as to a description of the e-CRF design, aiming to assist the researchers in selecting data for any particular analysis. The data accessed through Neurobot were linked to a separate repository for high temporal resolution ICU data, stored in customized HDF5 format.

High-quality data are critical to the entire scientific enterprise, yet the complexity and effort involved in data curation are vastly under-appreciated. This is especially true for large observational, clinical studies because of the amount of multimodal data that is captured and the opportunity for addressing numerous research questions through analysis, either alone or in combination with other data sets. Substantial efforts were implemented to ensure high quality of the CENTER data: First, automated data checks were built into the e-CRF system to alert investigators to impossible or improbable values and to detect inconsistent data entries, providing immediate feedback to investigators. Second, source data verification (SDV) of major characteristics was performed by ICON (Paris, France). SDV was performed in 100% of cases for informed consent and in 28% of patients for major characteristics on a total of 13448 data points. Third, a team of three dedicated personnel was employed full-time to check completeness and accuracy of entered data. Fourth, a Data Curation Task force (DCTF) was formed to perform data curation at a higher level. The DCTF team examined data, not only for missingness and plausibility, but also for multivariate consistency by crosschecking variables with other related concepts in the database. Derived variables were introduced and where data quality problems were identified, these were investigated to identify if these were structural issues (e.g. variances in datatype that was unanticipated at design time), site specific issues (e.g. unanticipated variances in data element interpretation due to local or language related misinterpretation) or simply isolated random errors. Data quality problems were addressed in three broad ways: first, for a small number of systematic data entry inconsistencies, it was possible to transform data or unify concepts across time points and documented plans were created for this. Secondly, where systematic issues were identified, there was a robust process involving a dedicated team to go back to sites to understand and identify problems and implement solutions (including for example process validation at source or ongoing training/needs analysis). Where common, but unsystematic errors were identified, e-CRF rules were updated and the subjects reflagged as being incomplete so that sites could go back and make corrections.

All these efforts have resulted in a high-quality database with highly granular data – the CENTER-TBI database consists of 2829 data elements, 8 versions of datasets with overall file storage exceeding 2.65 TB. We developed a detailed Data Dictionary with frequency tables to help guide researchers to navigate and understand the complex CENTER-TBI data (https://www.center-tbi.eu/data/dictionary).

The amount of work involved in the data curation process was much larger than anticipated and prompted further reflection and action. We recognized that lack of details concerning data curation methods can result in unresolved questions about the robustness of the data, its utility for addressing specific research questions or hypotheses and how to interpret the results. In collaboration with InTBIR partners, we developed the Data Acquisition, Quality and Curation for Observational Research Designs (DAQCORD) Guidelines (Ercole et al 2020). These are the first comprehensive set of data quality indicators for large observational studies. They were developed around the needs of neuroscience projects, but we believe they are relevant and generalisable, in whole or in part, to other fields of health research, and also to smaller observational studies and preclinical research.
The Neurobot system was used in most of the CENTER-TBI analyses and proved its value and robustness. The system is **adaptable to other disease states**. Although CENTER-TBI formally ended on March 31, 2021, continued availability of the Neurobot tool and access to the data are guaranteed for at least another year. We have additionally uploaded the CENTER-TBI data onto an OPAL platform, hosted by LUMC in Leiden (NL). Opal offers a secure and multi-project web-based application where data sources are transformed into target models based on flexible defined views and provides mapping to ontologies, thus complying to the FAIR principles. Access to the data is facilitated via a research dashboard and authentication server. This platform potentially provides all features for research including data processing, harmonization and mapping of data to common data models as well as (federated) analysis across datasets. Maintenance and access to this platform is guaranteed for at least 3 years.
These platforms offer opportunities for external researchers to access and use the unique data of CENTER-TBI and its repositories in the years to come. CENTER-TBI is open to data-sharing and welcomes proposals from other researchers, thus optimizing the use of public funding that supported CENTER-TBI and advancing the care for patients with TBI. We wish to ensure "good use" of the data, and have implemented a study- and publication proposal platform (https://www.center-tbi.eu/data). Proposals are reviewed by the Management Committee for scientific rigor and feasibility (not all research questions can be answered from the data). Following approval of the proposal and signing of a data use agreement, access can be granted. To date, over 375 proposals have been submitted by internal and external researchers. We have found this platform to serve an additional important purpose in **promoting collaborations** and limiting the risk of redundancy of efforts.

1.3.10 Networking activities and international collaborations in TBI (WP 16, 22).

TBI is a global problem that requires a global approach. We aimed to increase the scientific impact of CENTER-TBI by global collaborations, which offer opportunities for increasing patient numbers in joint analyses, strengthening research approaches, and provide a platform for involving the best scientists across the world. Specifically, we sought to foster collaboration with InTBIR partners, and to strengthen existing and initiate new collaborations on clinical TBI research worldwide. In addition, we welcomed proposals from external researchers to address research questions within the CENTER-TBI data and repositories, and established collaborations with industry. We present the multiple collaborations that CENTER-TBI developed outside of its core Consortium below:

Collaboration at the InTBIR level

The annual meetings of the International Initiative on TBI Research (InTBIR - http://intbir.nih.gov/), were attended by Lead investigators of CENTER-TBI, and our contributions based on ongoing work and emerging results from CENTER-TBI were extremely well received. Various investigators were active in the InTBIR working groups, and this led to a number of collaborative publications[3, 4, 5]. The platform provided by InTBIR is unique in bringing funders and researchers together on a regular basis and proved highly effective in stimulating networking and collaborations. From its inception in 2013, it was foreseen that the driving force provided by funding bodies would come to an end around 2020, when most major projects would be completed. InTBIR is currently transitioning towards a more investigator-driven initiative, and CENTER-TBI greatly welcomes the opportunity to take on a Lead role in the new organisation. Within the InTBIR group, CENTER-TBI developed close collaborations with TRACK-TBI (US), CREACTIVE (Europe) and developed the GAIN initiative on genetic analyses. Multiple interactions with TRACK-TBI occurred, led by the PI's Prof Andrew Maas/Prof David Menon (CENTER-TBI) and Prof Geoff Manley (TRACK-TBI). These interactions have led to the initiation of meta-analyses across the two studies, and plans to formalize these towards the future. A prime example of the strength of such collaborations is the validation performed by CENTER-TBI on a clustering analysis of CT phenotypes and their association to adverse outcome in mild TBI developed by TRACK-TBI. Results obtained in the two studies were virtually identical (Yuh et al 2021). Collaboration with CREACTIVE focussed on utilizing the Human Brain Project Medical Informatics Platform (HBP-MIP: https://mip.humanbrainproject.eu/) for a validation study on the Core IMPACT prognostic model across CENTER-TBI and CREACTIVE. Preliminary results demonstrated the potential of a tool like MIP to federate large databases in the field of TBI. Discrimination of the model across datasets was excellent, but substantial differences were noted in calibration. These could be explained by differences in case-mix between the datasets. However, we

also noted different approaches to scoring of some variables, highlighting the need for "deep harmonization" (see also section 1.3.8). The GAIN consortium (Genetic Associations in Neurotrauma) was formed to create a sufficiently large, high-quality, harmonized dataset of genetic, biomarker, imaging, and phenotypic data from victims of TBI with the aim to explore the influence of genetic variation on clinical outcome in TBI in a larger cohort than would be possible within the individual studies. Data from a provisional total of 5628 patients were included from 6 cohorts, providing the first GWAS/TWAS study in TBI (for details, see section 1.3.5)

Global collaborations

Collaborations with Australia, China and India resulted in linked data collections in these countries, using an identical data format as in CENTER-TBI (see also section 0). In **Australia (Melbourne 2 sites),** a total of 198 patients were recruited to the ICU stratum of OzENTER, and included in various comparative analyses which have to date resulted in three publications (Wiegers et al 2021 a,b; Gantner et al submitted). The collaboration with Australia was further intensified in the context of the MRFF Traumatic Brain Injury Mission Grant application, entitled "*An informatics approach to predict outcomes and monitor intervention efficacy following moderate to severe TBI*" which has been submitted by M. Fittzgerald with application number 2008223. Prof David Menon is a full Collaborative Investigator on this project and Prof Andrew Maas an Associate Investigator. Prof David Menon is also a full collaborator on another application on the same call, led by Prof Andrew Udy (*PRECISION-TBI – Promoting evidence-based, data driven care for critically ill moderate-to-severe TBI patients*). The **CENTER China Registry** collected data on patients with TBI admitted to hospitals across China in the same period and according to a similar format as the CENTER-TBI Registry. Data of 13138 patients from 52 hospitals in 22 provinces of China were analysed, and have resulted in 2 publications (Feng et al 2020; Gao et al 2020) with a third in preparation. Data collection in **India** was finalized with a total recruitment of 1017 patients to the Core study and 4903 to the Registry. The data have been transferred to the CENTER-TBI hub and are currently being curated, following which they will be entered into Neurobot. Comparative analysis between the European and Indian data will be performed in collaboration with our Indian partners. In collaboration with The Neurotraumatology Committee of the World Federation of Neurosurgical Societies and the NIHR Global Health Research Group (https://neurotrauma.world/) (Professors Peter Hutchinson and David Menon), actions have been initiated towards the development of a global TBI Registry. The ERANET-NEURON Initiative has enabled additional collaboration with European and Canadian partners. Prof Anne Vik (Trondheim) coordinated the TAI-MRI project (A New Traumatic Axonal Injury Classification Scheme based on Clinical and Improved MR Imaging Biomarkers), which includes members of WP 3 (Icometrix/UZA) and WP 8 (Cambridge) as co-applicants; while Prof David Menon (Cambridge, WP3 and WP5) coordinated the ICON-TBI Project (International Collaboration On Neuroinflammation in Traumatic Brain Injury), which involves collaborations between partners in Canada (Calgary), Italy (Milan), and the UK (Glasgow).

Collaborations with academic and industrial partners

Multiple interactions have occurred with both academic and industrial partners. A total of 33 study proposals have been received from external Parties, of which approximately half were accepted. Of these, external collaborations were formalized with in several fields:

<u>On Biomarker analyses:</u>

- ABCDx SA (Geneva, Switzerland): We shared 2083 sample aliquots in this collaboration with the aims of validating point-of-care assay, including GFAP, H-FABP and Il-10 2), and undertaking assays of inflammatory markers in a substantial number of patients.
- University of Örebro (Örebro, Sweden): 2000 residual serum aliquots (50µl) were shared in this collaboration, with the aim of undertaking metabolomic and lipidomic analyses. This was the first study on TBI that included lipidomic analyses, and showed that lipid metabolites in particular were associated with TBI severity and were among the strongest predictors of patient outcomes (for details, see section 1.3.5).
- NanoDx Inc. (formerly BioDirection) (Southborough, MA, USA): We shared 120 leftover serum aliquots (~100µl) in this collaboration to validate point-of-care assays for GFAP, UCHL-1, and S100B.
- University of Edinburgh (Edinburgh, UK): We shared 300 leftover serum aliquots (20µl), with the aim of exploring prognostic/diagnostic value of infrared spectroscopic analysis of serum blood samples.

<u>On Neuro-imaging</u>

- Biogen (Cambridge, MA, USA): The aim of this collaborations was to explore the relationship between contusion characteristics following TBI, namely the volumetric growth of the hemorrhage and edema compartments, with functional outcome measures at 90 and 180 days post-injury.

Embedded trials and associated studies

Embedded trials are defined as studies developed and initiated in collaboration with CENTER-TBI participants, addressing therapeutic interventions in CER trials. Associated studies refer to all other studies where principal investigators or sponsoring companies seek collaboration with CENTER-TBI – a potential win-win situation.
Embedded trials were

- *Thromboelastometry in Acute Hemorrhage Induced by Traumatic Injury of the Brain (TAHITI-B).* This pilot study provided preliminary evidence of efficacy and possible superiority of thromboelastometric over conventional coagulation tests, and has been published (Gratz et al 2019).
- *Randomised Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute SubDural Haematoma (RESCUE-ASDH).* This trial enrolled 836 patients from 52 centres in 13 countries. The database has been locked. Analysis is underway, and results are awaited.
- *Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury (POLAR-RCT).* This trial showed that prophylactic hypothermia compared with normothermia did not improve neurologic outcomes at 6 months
- *Protective Ventilatory Strategy in Severe Acute Brain Injury (PROLABI).* A publication was anticipated in 2020, but has been delayed by the problems with the SARS-CoV-2 pandemic in Italy.

Five additional projects sought linkage CENTER-TBI as associated studies but have not yet reached publication. We remain in contact with the researchers who submitted these proposals, with a request for acknowledgement of CENTER-TBI should they successfully publish details of their analysis. These studies focus on 1) post-acute neurosurgical interventions, 2) Paroxysmal Sympathetic Hyperactivity (PSH) post TBI, 3) sedative management in TBI, 4) EEG predictors of outcome, 5) fluid management in severe TBI. Overall, the number of **interactions and formalized collaborations** are substantial and have **added huge additional value** to the CENTER-TBI project.

1.3.11 Dissemination of study results and management recommendations for TBI to health care professionals, policy makers and consumers, aiming to improve health care for TBI at individual and population levels (WP 18, 19).

Dissemination aimed for widespread knowledge and use of research results by the target population e.g. policy makers, health care professionals and patients. Approaches included publications in the scientific literature, presentations and interactions with policymakers, press releases and media communications, social media accounts, and interactions through the CENTER-TBI website. Below, we summarize our main outputs.

Publications in the scientific literature

In terms of scientific output, the CENTER-TBI Consortium has been highly productive with – to date – over 200 publications in peer-reviewed scientific journals, of which 26 were in journals with an impact factor > 10.

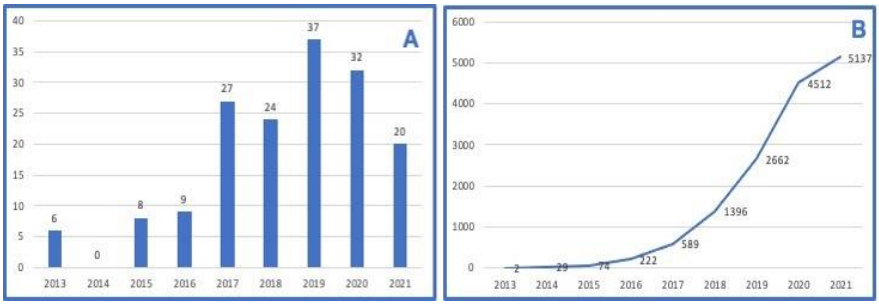


Figure 13: (A) Total publications per year and (B) cumulative number of citations from 2013-2021 (source: Web of Science, period of reference: Jan 1st, 2013 – May 18th, 2021).

Note: Number retrieved from Web of Science is lower than actual number of publications due to delays.

Over the years of the Project duration, the number of publications and their citations has steadily increased (Figure 13), leading to date to a total IF value of 1111, calculated as the summated Impact factor value of each publication. A complete list of all publications generated by the Consortium and CENTER-TBI affiliates is available on the CENTER-TBI website (https://www.center-tbi.eu/publications/), and in section 2.1 of this Report . All publications based upon the data collected during the CENTER-TBI studies included a list of Group Contributors. We strongly felt that all Participants and Investigator sites should receive academic credits for the work performed in and for CENTER. Without the input of all Investigators who collected data, analyses and scientific output would not have been possible. Whilst large Group Contributor lists are common in many fields of science, the inclusion of our list in the medical domain proved highly challenging, as these lists appeared to be irregularly picked up by PubMed,

the prime bibliography for medical domains. It first appeared that this varied by journal and could be related to the positioning of the Group Contributor list in the manuscript, e.g. at the end of the manuscript, in the acknowledgement section or in the supplementary material. It later turned out that PubMed changed their policy for extraction of authorship lists in 2016. Whilst prior that time, PubMed used to take care of this, working from information in the article or appendix listing, they stopped doing so without warning and pushed the work onto the Publishers. Some journals have the luxury of in-house production teams, but many do not. As a consequence, transfer of group Contributor lists to PubMed is often deficient. To alleviate these issues, the Lancet Journals, as example, now request authors to provide the names in a table clearly indicating forename and surname. The responsibility has therefore been shifted from PubMed to Publishers to authors – without any information on these changed procedures having been communicated to publishers or the broader academic community. To complicate matters even further, it turned out that academic bodies in some European countries, e.g. Norway, do not recognize Group Contributorship as meeting standards for obtaining academic credits. Some of the CENTER-TBI Investigators have suggested inclusion of principal investigators of high-enrolling sites in the main authorship listing. We did not consider this appropriate, as we strongly felt that all Investigators who contributed to the CENTER-TBI data should receive academic recognition for their efforts. **We conclude that the current system of academic credits in the field of medicine should be critically appraised and a common EU approach implemented.**

Interactions with Policymakers

Whilst publications in the scientific literature serve to improve the knowledge of and care provided by health care professionals, perhaps even greater advances can be obtained by implementing improvements at the policy level. CENTER-TBI developed various initiatives targeting policy makers. The publication of our Commissioned Issue on TBI in the Lancet Neurology (see also section 1.3.1) had a direct focus to inform policymakers on the huge burden posed by TBI to society, and summarized gaps in our knowledge. The Commission was presented at the European Parliament on Nov 7, 2017 – an occasion attended by a patient and his mother. Substantial advances in creating awareness for TBI at the policy level in the UK have been realized through the efforts of Prof David Menon in the All-Party Parliamentary Group on Acquired Brain Injury. This input drew heavily on the work undertaken in CENTER-TBI, and in particular the Lancet Neurology Commission on TBI, which was provided to all UK Members of Parliament in advance of discussions. A full report was published online on 18th Oct 2019, which concluded that The Government should bring together a taskforce to address the issues and recommendations as a matter of urgency (https://cdn.ymaws.com/ukabif.org.uk/resource/resmgr/campaigns/appg-abi_report_time-for-cha.pdf).

Media communications and press releases

CENTER-TBI has actively sought media attention by various initiatives. Press releases were broadly distributed around the presentation of the Lancet Neurology Commission at the European Parliament and the occasion summarized in a video (https://www.youtube.com/watch?v=VsUk_Q7qnWg). Forbes magazine featured the findings (https://www.forbes.com/sites/nicolefisher/2017/11/09/special-lancet-neurology-issue-targets-political-forum-to-combat-global-tbi/#59d4fd8675a8). CENTER-TBI attracted media interest across the globe, including Australia, China, Belgium, Germany, Hungary, Italy, the Netherlands, and the UK. EuroNews broadcast a special feature on CENTER-TBI in November 2019 (https://www.euronews.com/2019/02/25/i-was-not-who-i-was-researcher-into-new-care-for-traumatic-brain-injury-victims).

Social media

CENTER-TBI is present in Twitter (@CenterTBI) to inform the lay audience about the importance of TBI prevention and the results of the project. It also provides visibility to publications and scientific events where CENTER-TBI researchers are involved. The number of followers, mentions, and profile visits significantly increased over the course of the study, thus indicating a great interest in TBI both in clinicians who are not directly involved in the project and in lay audiences. During the report period, there have been 1312 tweets by 553 unique tweeters in 46 countries. This interest is widely diffused across the world showing that dissemination of our results exceeds the European boundaries (see Figure 14).

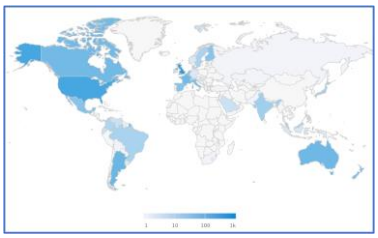


Figure 14: Countries with Twitter attention *(source: Altmetric Explorer)*

Public information platform

We developed and implemented an interactive public information platform explaining the impact and future developments of TBI research in lay language, within the public section of the CENTER-TBI website (https://www.center-tbi.eu/). This platform, active since month 13 after project start, aims to make the public active partners in research, clinical care, and policy development, provides links to patient organizations such as

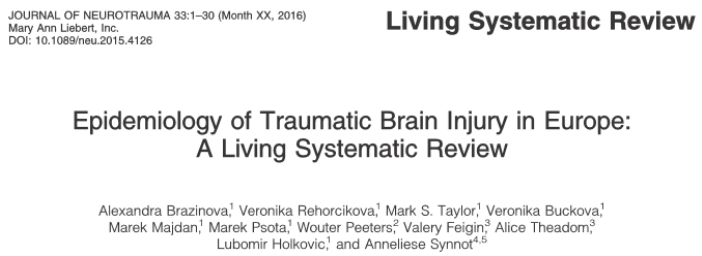
PatientsLikeMe (www.patientslikeme.com/), and includes a FAQ page. Development of a "knowledge commons" for TBI, integrating CENTER-TBI outputs into systematic reviews (WP18).

1.3.12 Development of a "knowledge commons" for TBI, integrating CENTER-TBI outputs into systematic reviews (WP18).

We established a "Knowledge commons" early on the project, consisting of the Partners involved in WP18. The Knowledge Commons was supported by a knowledge management project officer located at the National Trauma research institute (NTRI) and the Centre of Excellence in Traumatic Brain Injury Research in Melbourne. The aim was to develop a series of high-quality systematic reviews to summarize the evidence base underpinning our knowledge of TBI. The knowledge commons was responsible for overseeing the selection of systematic review topics, finding review authors, refining systematic review questions and instigating author training. We organized two three-day systematic review training courses (March 2014, Budapest and September 2015, Antwerp) for review authors, to which other interested researchers were also welcome.

We conducted a scoping review on trials in moderate and severe TBI, aiming to summarize the existing evidence from clinical trials, synthesize key RCT characteristics and findings, and determine their implications for clinical practice and future research (Bragge et al 2016). We identified 191 completed RCTs, of which only 26 (across 18 different interventions) were considered robust. Less than one-third of RCTs demonstrated low risk of bias. Less than a quarter of these RCTs used covariate adjustment, and only 7% employed an ordinal analysis approach. We concluded that considerable investment of resources in producing 191 completed RCTs for acute TBI management has resulted in very little translatable evidence. We further appraised the currency, completeness, and quality of evidence from systematic reviews (SRs) of acute management of moderate to severe TBI (Synnot et al 2018). A total of 85 SRs were identified, and of these less than half were judged as high quality (n = 38, 44.7%), and nearly 20% were low quality (n = 16, 18.8%). We concluded that a substantial number of SRs in acute management of moderate to severe TBI lack currency, completeness, and quality. Moreover, despite a substantial increase in number of systematic reviews, these are often outdated by the time they are published. The median time from primary study publication to its inclusion in a published systematic review ranges from 2.5 to 6.5 years. Considering the time required for conducting and publishing primary studies underpinning a systematic review, this means that by the time the SR is published, the information may already be over a decade old.

CENTER-TBI aimed to address this problem of lack of currency by introducing and pioneering the novel concept of **Living Systematic reviews (LSRs).** An LSR starts as a conventional SR, but then transitions into a "living" document, that is continually updated, incorporating relevant new evidence as it becomes available. By transforming the existing evidence into living reviews, the available evidence is optimized and remains current. A formal agreement was established with the chief editor and publishers of Journal of Neurotrauma. In brief, this agreement includes open access publication of the LSR's (subject to peer review) as a separate manuscript category with a specific tab labelled 'Living Systematic Review' (Figure 15).


JOURNAL OF NEUROTRAUMA 33:1–30 (Month XX, 2016)
Mary Ann Liebert, Inc.
DOI: 10.1089/neu.2015.4126

Living Systematic Review

Epidemiology of Traumatic Brain Injury in Europe:
A Living Systematic Review

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Figure 15: Example of a Living systematic review, designated as a specific manuscript category.

During the project, 5 LSRs have been published:

- Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review (Brazinova et al 2015).
- Adherence to Guidelines in Adult Patients with Traumatic Brain Injury: A Living Systematic Review (Cnossen et al 2021).
- Blood-based protein biomarkers for the management of traumatic brain injuries in adults presenting with mild head injury to emergency departments: a living systematic review and meta-analysis (Mondello et al 2021).
- Genetic Influences on Patient-Oriented Outcomes in Traumatic Brain Injury: A Living Systematic Review of Non-Apolipoprotein E Single-Nucleotide Polymorphisms (Zeiler et al 2019).
- The Apolipoprotein E4 polymorphism and outcomes from traumatic brain injury: a living systematic review and meta-analysis (McFadyen et al 2019).

Although literature searches can largely be automated, the maintenance and updating of LSRs required substantial efforts from the teams, and these efforts cannot all be continued after the end of the project. The development of LSR's, has now been taken forward in broader context by the Cochrane collaboration. We are proud that the

pioneering efforts of CENTER-TBI has contributed to the development of a **"new evidence ecosystem".** In addition, CENTER-TBI has published a total of 19 systematic reviews across a broad range of topics, ranging from methodological approaches and design features to high level ICU care. In combination, the LSRs and conventional systematic reviews constitute a **sound evidence base** summarizing current knowledge on TBI and its treatment.

1.3.13 Summary towards Global aims

The Global aims of CENTER-TBI were: [1] To improve characterization and classification of TBI; and [2] To identify the most effective clinical care, providing high quality evidence in support of treatment recommendations and guidelines. We addressed these aims using multiple strategies. These included:

- *A comprehensive assessment of the existing evidence base*. This resulted in authoritative reviews, including the development of conceptually new "Living Systematic Reviews". The Lancet Neurology Commission on TBI, led by the CENTER-TBI coordinators, now a core reference for researchers, funders, and policy makers.
- *Acquiring and analysing high quality, CDE-based, data* obtained in detailed longitudinal observational studies (CENTER-TBI Core Study and Registry).The Core study was combined with a neuro-imaging repository and DNA and biosample repositories. For analyses, we used state-of-the-art statistical approaches, machine learning techniques and convolutional neural networks.
- *Broadening the reach of CENTER-TBI* through Embedded Trials and Associated Studies to interact with other research in the EU, and addressing the global perspective with linked studies in Australia, China and India.
- *Undertaking Precision Medicine characterisation of TBI:* In order to support work on this aim we established the largest neuro-imaging repository and biosample bank in the world in the field of TBI. These resources enabled us to perform the first ever large-scale GWAS/TWAS study in TBI, conduct the first lipidomic study in TBI, and perform extensive biomarker analyses in hitherto unprecedented numbers.
- *Undertaking CER analyses:* CER analyses were underpinned by performing extensive provider profiling of participating centres and applying instrumental variable analyses. Analyses were challenging as between centre differences in outcome were lower than anticipated. Nevertheless, we clearly identified best practices, including recommendations for fluid management and venous thrombosis prophylaxis in the ICU.
- Providing a legacy database and neuroimaging and biosamples repositories for future research

Overall, CENTER-TBI has been hugely productive (over 200 publications) and provided many novel insights towards accomplishment of our global aims. Some highlights of results from these analyses include:

- Demonstration of the added value of biomarkers for triaging patients with mild TBI for CT scanning;
- Showing the added value of (advanced) MRI in characterizing TBI (particularly at extremes of the severity spectrum);
- Refining the use of advanced ICU monitoring in individualizing treatment;
- Providing recommendations for best practices
- Development of quality indicators

We identified epidemiological changes and disparities in care of direct relevance to policymakers and health care professionals. We also identified gender disparities in TBI outcome. Our Precision medicine pipeline clearly showed added value of the use of emerging technologies and resulted in a novel multidimensional classification for initial injury severity and recommendations for the targeted application of selected outcome instruments in multidimensional approaches to outcome assessment. Our CER pipeline delivered recommendations for best practices in the ICU setting, and identified room for improvement in various aspects of care delivery and care paths. An overview of our findings and their impact on care and research is provided in section 1.4.6.

In summary, CENTER-TBI has accomplished what it set out to do and produced many results of direct relevance to citizens and patients, to policymakers, health care professionals and researchers alike. Formally, the project period ended on 31st March 2021. There will, however be "life after/with" CENTER-TBI: The clinical database and associated repositories constitute a unique and extremely rich resource which will enable addressing additional research questions both by CENTER researchers and external groups. Our plans include a major focus on meta-analysis between CENTER-TBI and other IntBIR studies. Initial analyses between CENTER- and TRACK-TBI are already being undertaken with own resources. We have accrued additional funding that will guarantee access to and maintenance of the CENTER data with options for support of data analyses. However, this funding will be insufficient to fully perform the required "deep harmonization" (see section 1.3.8) in preparation of federated meta-analyses and to subsequently perform detailed analyses. We are actively seeking support to realize the full potential of meta-analyses across studies and will be applying for definitive funding in partnership with TRACK-TBI in Q3 2021.

1.4 Potential impact

1.4.1 Background

TBI is a substantial global public health challenge. The annual global incidence of TBI is over 50 million, and it is estimated that about half the world's population will sustain one or more TBIs at some point in their lifetime. Globally, TBI is a major cause of death and disability across all ages, and kills more young adults than any other disease. Survivors of TBI can be left with significant disability: at six months post-injury, half of survivors of severe TBI are severely disabled, and even with a mild TBI, 50% fails to make a complete recovery. TBI has a substantial impact in all countries, but imposes a disproportionate burden of disability and death in low- and middle-income countries (LMICs). It has been estimated that TBI costs the global economy approximately €325 billion annually, which means that around one in every €150 that the world makes is spent on the costs or consequences of TBI. Despite the magnitude of the problem posed by TBI, and its clear impact over many decades, efforts to tackle the problem have been fragmented and under-resourced, and the clinical care of TBI has been suboptimal. CENTER-TBI, along with other partners in the International Traumatic Brain Injury Research (InTBIR) initiative, was conceptualised as a means of generating knowledge that could contribute to reducing the individual, public health, and societal burden of TBI.

1.4.2 The CENTER-TBI study – matching study structure and outputs to desired impact

Details regarding the CENTER-TBI study are provided in section 1.2 of this report. The current discussion focuses on those aspects and approaches of the study that enabled us to deliver the impact we aspired to. CENTER-TBI addressed both broader issues of health care organisation for TBI, and more detailed aspects related to characterization and best clinical practices. We aimed to capture the "real world situation" in order to provide broadly applicable recommendations. This holds the greatest potential to improve current health care for TBI and its delivery at both population and individual levels. Key aspects of CENTER-TBI that are of relevance to our discussion of impact include:

Landscape of TBI care and research: Systematic Reviews and the Lancet Neurology Commission on TBI: Prior to start of CENTER-TBI, we identified major gaps in our knowledge and research priorities which informed our plans for the study. This analysis was subsequently consolidated in the form of systematic reviews, many of which used the novel methodology of Living Systematic reviews. Subsequently, the CENTER-TBI Coordinators (Maas & Menon) were invited by the Editors of the Lancet Neurology to lead a Commission on TBI, which was published in 2017, and is now a core reference resource for clinicians and researchers who work with TBI.

The CENTER-TBI Core study: The core study (in the EU and Israel) recruited ~4509 patients, expanded through recruitment in India and Australia to a total of 5726 patients. These patient numbers ensured that the study was appropriately powered for our planned analysis, and collected data with sufficient granularity to enable Precision Medicine and Comparative Effectiveness Research analyses of patient endotypes (clusters of patients with common presentation, disease course and outcome), and common interventions, respectively. We also ensured that the granular data collection included novel methods (advanced neuroimaging, high resolution ICU monitoring, blood biomarker measurement, and genomics), so that any definition of patient endotypes could move beyond existing schemes of classification based on the Glasgow Coma Score (GCS) as mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS $\leq$8) TBI, or broad pathoanatomical categories based on computed tomography (CT) scanning.

The CENTER-TBI Registry: The CENTER-TBI registry (which comprised 22,849 patients from the EU and Israel, supplemented by patients from India and China to a total of 41,367 patients) collected far less granular data than the core study. However, it was important to explore broad epidemiological issues, and to address the effects of differences in systems of care. The effects of broad variations in care was also facilitated by the Provider Profiling exercise that we undertook, which characterised system and process variations in participating centres. In addition, comparison with the Core study data in each centre (and with collaborating national TBI audits) provided an excellent framework to assess generalisability of our study results, both nationally and internationally

The CENTER-TBI Database, Repositories and novel research tools: As part of our recruitment of patients to the Core study, we created a well curated and accessible database of clinical data, readily accessible through a novel tool created by INCF as part of the study (Neurobot). The CENTER- TBI study has also resulted in the largest biorepositories in the world for neuro-images (CT and MR images) and blood/serum samples for TBI. The establishment of these biorepositories and a well-characterized clinical database will facilitate legacy research extending well beyond the duration of this project. We developed several novel methodologies and tools, including

AI based lesion and anatomical segmentation on CT and MR images, and FDA-approved diagnostic pipelines. These have been made widely available for academic use or developed as commercial pipelines.

Promoting European, global, and academic-commercial collaboration: The CENTER-TBI dataset and repositories not only represent a valuable legacy resource, but also provide an important vehicle for ongoing collaboration as the study proceeded. Well characterised models of collaboration, including the use of Analysis and Publication summaries on the CENTER-TBI website, a mechanism for review of study proposals submitted by internal and external investigators, and practical Data Use Agreements, have all facilitated access to the rich data and sample repositories by investigators not originally part of CENTER-TBI. Many of these are new academic collaborators, while others are commercial entities particularly interested in biomarker development and study design for novel therapies. At a global level, CENTER-TBI has been one of the two main partners in InTBIR, driving internationalisation of CDEs, harmonisation of data, and joint analyses across studies.

1.4.3 Gaps in knowledge and Research priorities

Below, we first summarize gaps in current knowledge and research priorities identified at the start of the project (Table 5). We then align these to key recommendations that we made in the Lancet Neurology Commission on TBI. This analysis provides a context to subsequent parts of this section where we describe the structured approach we used to evaluate the impact of our findings, our dissemination activities, and exploitation of results.

Table 5: Gaps in knowledge and research priorities (from CENTER-TBI application)

Gaps in knowledge	Research Priorities
Lack of strong evidence for treatment recommendations	Comparative Effectiveness Research to determine the benefits of current and new treatments/interventions
Antiquated, unidimensional and insensitive approaches to classification of initial severity and outcome	Multidimensional classification system to enable targeted therapies
Understanding different responses to similar injuries	Prediction of outcome by patient and injury characteristics, and the quality of general and specific management across the continuum of care.
The importance of pre-morbid factors and co-morbidities	Determination of the effects of age, co-morbidity and their interaction with cognitive reserve and cerebral atrophy after a brain injury.
Absence of validated performance indicators	Development of methods for defining and measuring quality of care

These gaps in knowledge, summarised in the CENTER-TBI funding application, were developed and refined as part of the Lancet Neurology Commission on TBI (http://www.thelancet.com/commissions/traumatic-brain-injury). The scope of the Commission was somewhat wider than our aims in CENTER-TBI, but there was substantial concordance in those sections of the recommendations that mapped onto our research plans. These sections, with the cognate recommendations that we made in in each case, are listed below in Table 6. In some instances, the recommendations are amplified by commentary from the text of the CENTER-TBI application or the broader text of the TBI Commission.

Table 6: Recommendations from the Lancet Neurology Commission (in blue text) on TBI in areas of direct relevance to CENTER-TBI, and additional implications (*in italics)* that were addressed in CENTER-TBI

Area of relevance	Recommendations from the Lancet Neurology Commission on TBI (and additional implications, where appropriate)
Systems of care for TBI:	Health-care policies should aim to improve access to acute and postacute care to reduce the effects of TBI on patients, families, and society. *Provision of post-acute care needs to address patients with mild TBI as well as those with more severe injuries.*
Clinical management of TBI:	Robust evidence is needed to inform guidelines on medical, surgical, and rehabilitation interventions, and hence improve outcomes for patients with TBI. *In addition to conventional randomized clinical trials (RCT), such evidence will be informed by epidemiological associations and comparative effectiveness research (CER)*
Characterisation of TBI: the path to Precision medicine:	Research is needed to improve the precision of diagnosis, classification, and characterisation of TBI using multidomain approaches. *Such classification needs to go beyond conventional approaches used to date, and make use of advanced neuroimaging, genomics, biomarkers, and novel methodology*
Assessment of TBI outcome – towards multidimensional approaches:	Multidimensional outcome constructs that quantify the overall burden of disability from TBI need to be developed and validated to guide improved clinical management and support high-quality research. *Such comprehensive outcome assessment must address practice variations, and be flexible enough to account for the entire spectrum of TBI outcomes.*
Prognosis in TBI – linking patient and injury characteristics to outcome:	Efforts are needed to develop a set of quality indicators for TBI that includes structure, process, and outcome metrics. *Currently, there are no TBI-specific indicators.*
New directions for acquiring and implementing evidence:	Comparative effectiveness research should be supported to identify best practices and to improve the level of evidence for systems of care and diagnostic and therapeutic interventions. *CER provides a valuable adjunct to conventional RCTs to seek evidence in areas where such trials are difficult to set up, and to set hypotheses for confirmation by subsequent trials*
Coordinated research efforts on a global basis:	A commitment of governmental and non-governmental funding bodies, as well as industrial partners, is needed to foster global collaborations and to establish national and international biorepositories and databases that could facilitate future TBI research. *This implies the need to develop a common vocabulary and syntax for describing phenotypic characterization of TBI: Common data Elements (CDEs)*

1.4.4 A framework for describing the impact of CENTER-TBI

In our funding application, we structured our assessment of the potential impact of CENTER-TBI using a framework provided by the 2014 UK Research Excellence Framework (REF). The updated UK REF exercise (https://www.ref.ac.uk/publications/panel-criteria-and-working-methods-201902/) uses similar broad measures of impact assessment, but both have disadvantages, since they sought to parse impact across a broad range of academic endeavour – ranging from art and humanities, through physical and biological sciences, to clinical medicine and social sciences. These issues have been considered by other bodies, including the International School on Research Impact Assessment (ISRIA)[6]. ISRIA provides a useful framework, originally used by Alberta Innovates7, which more specifically addresses Impact Assessment in healthcare research. We therefore chose to structure our current analysis of impact according to ISRIA Framework (Table 7).

Table 7: Proposed ISRIA framework for impact assessment for healthcare research

Impacts	Indicators
Capacity-building	Leveraged funding, research tools and methods, use of facilities and resources, career trajectory of researchers
Advancing knowledge	Bibliometrics, engagements, esteem measures, collaborations and partnerships
Informing decision-making	Influence on policies, practices, products, processes and behaviours (both in health and the determinants of health)
Health	Medical and health interventions, health quality indicators, health status
Economic and social benefits	Intellectual property and licensing, spin outs, economic returns, jobs, economic diversity and productivity
Social engagement	Public involvement, dissemination, engagement with relevant patient or commissioning groups, culture and creativity

Regardless of the framework used, it is important to identify the stakeholders who will experience the benefits of such impact, since a broad consideration of these target groups will allow a more rational assessment and allocation of potential impact.

1.4.5 Stakeholders: Beneficiaries of impact from CENTER-TBI

A wide range of stakeholders could potentially benefit from the outputs of CENTER TBI. These include:

- *Citizens/Patients*: While the conventional description of this class of stakeholders/beneficiaries would be patients, we have chosen to use the term "citizens" since some of the epidemiological insights provided by CENTER-TBI may result in policies that prevent TBI, and hence prevent citizens ever becoming patients. In addition, our data suggest that individuals who sustain a TBI may exit the acute illness and be discharged from clinical care. Though such individuals are not seen as patients at that stage, our data suggest that a significant proportion have ongoing healthcare needs which are currently poorly addressed.
- *Health care professionals and Researchers*: Improvements in diagnosis, comparative effectiveness research, and characterisation of disease endotypes are all targeted outcomes from CENTER-TBI. If realised, these could provide more rapid and individualised treatments for patients through improved and harmonised guidelines – thus achieving the goal of precision medicine. The increases in knowledge delivered by CENTER-TBI provide a basis for setting new hypotheses which can be tested in subsequent clinical studies, while the clinical data, neuroimaging repositories, and biosample resources provide a rich substrate for secondary analysis and research. In addition, the novel insights obtained from analyses of clinical data could also inform basic research in a "bedside to bench" reverse translational pipeline.
- *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 organisational aspects of care delivery could yield substantial benefits. 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.

1.4.6 Impacts achieved

Here we summarize the impact of CENTER-TBI using the domains of the ISRIA Framework.

Capacity building

1) *Leveraged funding:* CENTER-TBI was a large scale collaborative project, supported by the FP7 Program of the European Union (Grant No 602150). We leveraged this funding by obtaining additional support from OneMind (US), the Hannelore Kohl foundation (DE), IntegraLifeSciences (US) and NeuroTrauma Sciences (US). OneMind was instrumental in supporting the development and implementation of the e-CRF, data collection procedures and the development of Neurobot, our data access tool. The Hannelore Kohl Foundation supported data collection and analyses by centres in Germany, and facilitated an extended Registry data collection in German sites. IntegraLifeSciences provided additional support towards the data curation. NeuroTraumaSciences provided support towards analyses, in particular during the no-cost

extension period and will provide further support to maintain the CENTER-TBI infrastructure and to facilitate further data mining after the formal end of the FP7 funding period. In addition, CENTER-TBI participants have also been successful in securing follow on grants from the ERANET-NEURON program (see later)

2) *Research tools*: CENTER-TBI developed *and* implemented the following research tools:
   - Translation, linguistic validation and psychometric evaluation of outcome instruments. In total, 237 translations and 211 linguistic validations were carried out in up to 20 languages; all are accessible in the public domain on the website of CENTER-TBI (https://www.center-tbi.eu/project/validated-translations-outcome-instruments/). We consider this a major output of CENTER-TBI as they provide a solid basis for future TBI research and clinical practice and allow for aggregation and data analysis across different countries and languages.
   - A GOSE manual: Interactions in InTBIR highlighted variations in GOSE application by different groups. CENTER-TBI and TRACK-TBI collaborated to produce a definitive manual for its use (Wilson et al 2021).
   - Support tool for Database access: Neurobot (details available on the SciCrunch Resource Identification Portal; Research Resource Identifier RRID/SCR_017004). This bespoke data access tool was developed and regularly updated by KI-INCF (Stockholm SE) - a substantial task given the large number and types of variables, and the inclusion of continuous and longitudinal data.
   - Study- and publication proposal platform (https://www.center-tbi.eu/data). We implemented a study- and publication proposal platform (SPP) on the CENTER-TBI website. We wished to ensure "good use" of the data, promote collaborations and prevent redundancy of efforts. Proposals are reviewed by the Management Committee for scientific rigor and feasibility. To date, over 300 proposals have been submitted by internal and external researchers. All accepted proposals are listed on the website to be accessible in the CENTER-TBI community and the platform will remain operational in the upcoming years for further data sharing. We have found this platform to serve an additional important purpose in **promoting collaborations** and limiting the risk of redundancy of efforts.
   - icobrain tbi (https://icometrix.com/services/icobrain-tbi): This tool offers automated reporting of acute CT scans in TBI, including automated volumetric analyses. It received FDA clearance 510(k) in Nov 2018.
   - Ico**mpanion** is an app, originally developed by ico**metrix** for self-reporting of outcome in patients with multiple sclerosis **(**https://icompanion.ms/) has now been expanded to include specific outcome domains relevant to TBI. This app provides patients with the opportunity to report their perception of outcome on a frequent basis.
   - BLAST CT is a deep learning automated pipeline for lesion detection,segmentation, and quantitation in CT images following TBI, freely available on Github (https://github.com/biomedia-mira/blast-ct).

3) *Career trajectory of researchers*: CENTER-TBI provided a unique platform for stimulating the career of researchers and promoting interactions between research groups. We provided courses on evidence-based medicine and methodology for systematic reviews, and offered scholarships in conjunction with scientific societies to attract the best and brightest young researchers to neurotrauma and facilitate EU wide mobility by providing opportunities to work at leading TBI centres that participate in the project. A total of 7 PhD theses were successfully completed during the Project, and there are more in the pipeline.

4) *Global standards*: Standardisation of data collection is essential for research and the common data elements have shown their great value in IntBIR projects, including CENTER-TBI and its linked studies. However, they are currently mainly US-centric, and we identified major issues with regard to global application, including violation of privacy regulation. We conclude that efforts should be supported to upgrade the primarily US centric common data elements to global standards.

Advancing knowledge

CENTER-TBI was all about "advancing knowledge" on TBI and improving its treatment. Detailed information on "Game-changing" findings and recommendations are provided under the headings "Informing decision-making" and "Health" of this section. Here, we summarize the impact in terms of *collaborations and bibliometrics*.

1) *Collaborations:* Collaborations were fostered at the InTBIR level, with academic and industrial partners, and in a global context.
   - IntBIR: CENTER-TBI was very active within IntBIR, participating in annual meetings, and being actively involved in various InTBIR working groups. IntBIR is currently transitioning to a more investigator-driven organization, and Prof David Menon (co-coordinator of CENTER-TBI) will likely become one of the co-leads. Within IntBIR, close collaborations exist with TRACK-TBI ("sister" study in the US to CENTER)

and with CREACTIVE. We have utilized the Human Brain Project Medical Informatics Platform (HBP-MIP: https://mip.humanbrainproject.eu/) platform for a validation study on the Core IMPACT prognostic model across CENTER-TBI and CREACTIVE. We established the GAIN consortium (Genetic Associations in Neurotrauma) to explore the influence of genetic variation on clinical outcome in TBI in a larger cohort than would be possible within the individual studies. Data from a provisional total of 5628 patients were included from 6 cohorts: CENTER-TBI (n=3187), Cambridge (n=575), Turku (n=157), TRACK-TBI (n=1672), Mass general Brigham (n=409) to produce **the first GWAS/TWAS study in TBI**.

- Academic and industrial partners*:* Multiple interactions have occurred with both academic and industrial partners. A total of 33 study proposals have been received from external Parties, of which approximately half were accepted. Collaborations were formalized for biomarker analyses with the Universities of Edinburgh (Scotland) and Örebro (Sweden) as academic partners, and with ABCDx (Geneva, Switzerland) and NanoDx (Southborough, MA, USA) as industrial partners. We further established collaboration with Biogen (Cambridge, MA, USA) to explore the relationship between contusion characteristics and functional outcome.
- Global collaborations: Collaborations with Australia, China and India resulted in linked data collections (OzENTER: ICU stratum n=198); CENTER China Registry: n= 13138); India Core study: n=1017 and Registry: n=4903) using a similar data format as in CENTER-TBI, illustrating the global outreach of CENTER and highlighting the relevance of global data collection standards (CDEs).We established additional collaborations with European and Canadian partners through ERANET-NEURON(see also section 1.3.10).

2) *Bibliometrics:* CENTER-TBI has produced over 200 publications in peer-reviewed scientific journals to date.

Informing decision-making

Our large dataset, highly granular data collection, and advanced use of methodologies has allowed us to make important recommendations that are of relevance to a wide range of stakeholders. We list the key recommendations/conclusions below, and designate the stakeholders for whom the recommendation has impact relevance (**CP:** Citizens/Patients; **PoI**: Policymakers; **HC**: Health care professionals and researchers):

1) **Health Care systems need to address the needs of older patients with TBI, and research should be stimulated to provide evidence in support of their treatments.** *Justification:* TBI is a major cause of death and disability across all ages. In the EU, approximately 1.5 million patients are admitted to hospital each year for TBI. The epidemiology of TBI has changed: Median age is currently 50-55, and 28% are over 65 years of age – a substantial increase compared to one or two decades ago. Older patients have more comorbidities with associated medication. In the Core study, 11% had serious co-morbidities, that can adversely affect disease course. *Both* the CENTER Core study and the CENTER China registry showed that pre-injury use of anticoagulants is associated with higher mortality. The needs of older patients for post-acute care are different from younger patients. Most clinical trials to date have excluded patients > 65 years of age, and as a consequence little evidence exists to support their treatments. (*Impact: CP/PoI/HC*)
2) **High energy transfer mechanisms should be de-emphasized for injury scene and ED triage of older people with TBI.** *Justification:* We found that 40% of patients with TBI are injured by low energy falls. These mostly occur in older patients, and have similar rates of CT brain scan abnormalities and in-hospital mortality as those injured by other mechanisms, but are 50% less likely to receive critical care or emergency interventions. (***Impact: PoI/HC*).**
3) **Alcohol prevention campaigns should be expanded to increase awareness of the risk for serious injury from falls under the influence of alcohol.** *Justification*: We found that alcohol use was reported in 28% of patients injured by incidental falls versus only 17% of those injured in road traffic incidents. These findings further illustrate the success of traffic-related alcohol prevention campaigns. (***Impact: CP/PoI/HC*).**
4) **Alcohol and substance abuse are major factors in violence-related TBI.** *Justification:* Alcohol use was reported in 64% and cannabis use in 15% of violence-related TBI. **(*Impact: CP/PoI/HC*).**
5) Litigation procedures should not consider a normal CT scan at presentation as evidence of absence of structural brain damage, let alone absence of TBI. *Justification:* Our MR studies showed that 30% of patients with mild TBI and a normal CT scan demonstrated structural abnormalities on MR imaging. Moreover, at least in univariate analysis, serum levels of the brain-specific biomarker NFL were found to be significantly higher ($p<0.05$) in patients with mTBI and a normal CT scan on presentation who had residual complaints at 6 months, compared to those who had a full recovery, and this difference remained for samples obtained at 2-3 weeks. (*Impact: CP/PoI*).

6) **Substantial health-economic benefits can be accrued by improving the care delivery (in particular structured follow-up) and developing new treatments for mTBI.** *Justification:* Mild TBI is the most common form of TBI (82% in the CENTER-TBI registry) and poses the largest burden to patients and society. "Mild" TBI is not so mild: We found that 63% of patients report residual disability or complaints at 6 months after injury: 51% had a GOSE below 8, around 25% SF12v2 summary scores below threshold for impairment (scores <40) and 26% had RPQ scores ≥ 16, indicating significant postconcussion sypmtoms. Despite these high impairment rates, 90% of centres do not routinely schedule a follow-up appointment on discharge home from the Emergency Room after mild TBI, and only 46% do so on discharge of patients with mTBI from the ward. **(*Impact: CP/Pol/HC*).**
7) **Access to and provision of care for individuals with moderate to severe disabilities after TBI needs to be improved. Health care systems should anticipate an increased need for rehabilitation after TBI** *Justification:* Data on 1206 individuals enrolled into CENTER-TBI who had moderate to severe disability at 6 months after injury showed that 90% reported rehabilitation needs, but only 30% received in-patient rehabilitation and 15% out-patient rehabilitation. We found a much lower between-centre variation in mortality (MOR:1.2) compared to previous studies, and in patients with moderate to severe TBI mortality was lower than predicted from the IMPACT prognostic model (observed to expected ratio 0.70 [0.62– 0.76]), but unfavourable outcome (defined as a GOSE<5), was not (1.06 [95% CI 0.97– 1.14]). These data suggest that treatment has improved with fewer deaths, but at a cost of more survivors with disability. **(*Impact: CP/Pol/HC*).**
8) **Efficiency of use of ICU resources may be improved by increasing resources to manage mild-TBI outside ICUs** *Justification:* We found that 36% of patients admitted to the ICU with TBI are classified as "mild" TBI. Some of these are motivated by the presence of serious extracranial injuries, by secondary deterioration or by a substantial risk for deterioration due to possible progression of traumatic intracranial lesions, but it appears likely that ICU admission is motivated in some by lack of resources on other wards. **(*Impact: Pol/HC*).**
9) **The co-occurrence of TBI with injuries to other parts of the body emphasizes the need for a multidisciplinary approach to treatment.** *Justification:* Major extracranial injuries (abbreviated injury score ≥3) were reported in 422 (28%) patients in the admission stratum and in 1174 (55%) in the ICU stratum. The body region most commonly injured was thorax and chest (n=742 [35%]), and concomitant serious spinal injuries occurred in 374 (18%) patients. **(*Impact: HC*)**.
10) **Quality indicators should be used to benchmark quality of care between institutions.** *Justification:* We have validated Quality Indicators to support benchmarking and quality improvement programs (**Impact to *Pol/HC*)**.

Health

The conclusions that we detail below also translate into important insights for clinicians and researchers, which will inform ongoing patient management and research in TBI

1) The biomarker GFAP should be included in decision rules for triaging patients with mild TBI for CT scanning. In patients with mild TBI, GFAP showed incremental diagnostic value: discrimination increased from 0.84 [95%CI: 0.83-0.86] to 0.89 [95%CI: 0.87-0.90] when GFAP was included. Combinations with other biomarkers showed no added value. These results further challenge the utility and cost effectiveness of combined biomarker assays.
2) The estimated heritability in our GWAS studies was 0.28, suggesting that common genetic variation significantly contributes to inter-individual variability in host response and outcome.
3) Qualitative MR imaging adds to the accuracy of outcome prediction beyond conventional clinical and CT characteristics, and quantitative volumetric MRI and DTI metrics provides further added value.
4) DTI metrics can help predict emergence from coma in patients with very severe disturbances of consciousness.
5) Criteria for in-hospital intubation should be broadened to include patients with a GCS of 9 or 10.
6) Early tracheostomy (within one week) for patients requiring ventilator support is associated with better outcome and reduced length of stay in hospital and ICU.
7) The recommended threshold in the Guidelines of 22 mmHg for treating raised intracranial pressure is not absolute. We found a threshold of 18 +/- 4 mm Hg.
8) Treatment for raised ICP should be individualized, taking autoregulatory status into account.
9) Maintaining a neutral fluid balance in ICU patients is associated with better outcome, but is not common practice. We found an increased for poorer outcome per 0·1L increase of fluid balance with an OR of 1·10 [95%CI:1·07–1·13] for ICU mortality and 1·03 [95%CI:1·02–1·05] for functional outcome.

10) Outcome predictors differ between mild and moderate/severe TBI. In mod/severe TBI, outcome is mainly dependent on injury severity, whilst in mild TBI it is more "what the patient brings to the injury" (e.g. pre-injury health and psychiatric history). Existing models for predicting outcome in mod/severe TBI were validated and updated and a new model for mild TBI developed.

Economic and social benefits

Many of the outputs of CENTER-TBI, described under the headings "Informing decision-making" and "Health" carry the potential for substantial economic and social benefits. For example, we identified various disparities in care provision for patients with TBI (e.g. needs of older patients, lower care for patients injured by low energy mechanisms, lack of structured follow-up and post-acute care for patients with mild TBI, rehabilitation needs for patients with moderate to severe disability), and addressing these will result in large economic and social benefits. We also identified **gender disparities** in outcome after mild TBI. Whilst males are more prone to TBI, compared to men, women with mild TBI had worse outcomes (OR 1.4, 95% CI: 1.2-1.6), lower generic and disease-specific HRQoL, and more severe PCS, depression, and anxiety.

Social engagement

1) *Public information platform:* We developed and implemented an interactive public information platform explaining the impact and future developments of TBI research in lay language on the CENTER-TBI website (https://www.center-tbi.eu/). This platform aims to make the public active partners in research, clinical care, and policy development, and provides links to patient organizations, such as PatientsLikeMe (www.patientslikeme.com/). Patient requests have frequently been received and answered about disease characteristics, rehabilitation possibilities and referrals to TBI specialists worldwide. Interestingly, various of these requests originated from outside Europe. This illustrates the great need of patients across the world for guidance and help in seeking appropriate treatment for their TBI.
2) *Media attention:* CENTER-TBI has actively sought media attention by various initiatives. Press releases were broadly distributed around the presentation of the Lancet neurology Commission on TBI at the European Parliament and the occasion summarized in a video (https://www.youtube.com/watch?v=VsUk_Q7qnWg). Forbes magazine featured the findings (https://www.forbes.com/sites/nicolefisher/2017/11/09/special-lancet-neurology-issue-targets-political-forum-to-combat-global-tbi/#59d4fd8675a8). CENTER-TBI attracted media interest across the globe, including Australia, China, Belgium, Germany, Hungary, Italy, the Netherlands, and the UK. EuroNews broadcast a special feature on CENTER-TBI in November 2019 (https://www.euronews.com/2019/02/25/i-was-not-who-i-was-researcher-into-new-care-for-traumatic-brain-injury-victims). Public engagement was specifically sought in the UK by the All-Party Parliamentary Group on Acquired Brain Injury. A full report (Executive editor: Prof David Menon, joint coordinator of CENTER-TBI) was published online on 18th October 2019 (https://cdn.ymaws.com/ukabif.org.uk/resource/resmgr/campaigns/appg-abi_report_time-for-cha.pdf).
3) *Social media:* CENTER-TBI is present on Twitter (@CenterTBI), providing visibility to publications and scientific events where investigators and other clinicians interested in CENTER-TBI are involved. The number of followers, mentions and profile visits has significantly increased during the years, and interest is widely diffused across the world showing that dissemination of our results exceeds the European boundaries.

1.4.7 Dissemination and exploitation

1) *Knowledge Commons:* Within CENTER-TBI we established a "Knowledge commons" with the aim to develop high-quality systematic reviews to summarize the evidence base underpinning our knowledge of TBI. We conducted a scoping review on trials in moderate and severe TBI, and published 19 systematic reviews and 5 Living systematic reviews (see section 1.3.12). CENTER-TBI pioneered the implementation of Living systematic reviews, in which the evidence is continually updated, incorporating relevant new evidence as it becomes available. These pioneering efforts have contributed to the development of a **"new evidence ecosystem"**, that is currently being pursued by the Cochrane Collaboration.

1) *Dissemination of study results:* Dissemination aimed for widespread knowledge and use of research results by the target population. We conducted a range of approaches targeting policy makers, health care professionals and patients. Approaches included publications in the scientific literature, presentations and interactions with policymakers, press releases and media communications, social media accounts, and interactions through the CENTER-TBI website (see also section 1.4.6). Here, we focus on dissemination in the scientific literature. The CENTER-TBI Consortium has been highly productive with – to date – **over 200 publications in peer-reviewed scientific journals**, of which 26

were in journals with an impact factor > 10. A complete list of all publications generated by the Consortium and CENTER-TBI affiliates is available on the CENTER-TBI website (https://www.center-tbi.eu/publications/). CENTER-TBI was designed as team collaborative effort, and most publications spanned various research groups. Figure 16 displays a graphical presentation of the interactions between authors from the various CENTER-TBI research groups.

2) *Exploitation:* We developed and implemented an open standards-based platform (Neurobot) for the collection and storage of clinical data and neuroimaging and biomarker results based on Common Data Elements (CDEs). Collaborative analytics are facilitated by providing standard interfaces to the platform through which various analytics tools can access the data. A second platform (Opal) was implemented, offering additional analytical tools and options to facilitate meta-analyses across different studies. These platforms offer opportunities for external researchers to access and use the unique data of CENTER-TBI and its repositories in the years to come. CENTER-TBI is open to data-sharing and welcomes proposals from other researchers, thus optimizing the use of public funding that supported CENTER-TBI and advancing the care for patients with TBI. The linguistically validated translations of outcome instruments in up to 20 languages are accessible in the public domain on the website of CENTER-TBI (https://www.center-tbi.eu/project/validated-translations-outcome-instruments/), and provide a solid basis for future TBI research and clinical practice in international settings. Icobrain tbi, developed for automated segmentation and volumetric analyses of CT images, received FDA clearance 510(k) in November 2018 and now offers radiologists, neurosurgeons, and neurologists easy access to clinically important metrics to better characterize and inform management of TBI in the acute clinical setting.

References:

CENTER-related citations are marked in blue in the text and can be found on the CENTER website.

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2) MRC CRASH Trial Collaborators, Perel P, Arango M, Clayton T, Edwards P, Komolafe E, Poccock S, Roberts I, Shakur H, Steyerberg E, Yutthakasemsunt S. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ. 2008 Feb 23;336(7641):425-9. doi: 10.1136/bmj.39461.643438.25. Epub 2008 Feb 12. PMID: 18270239; PMCID: PMC2249681.
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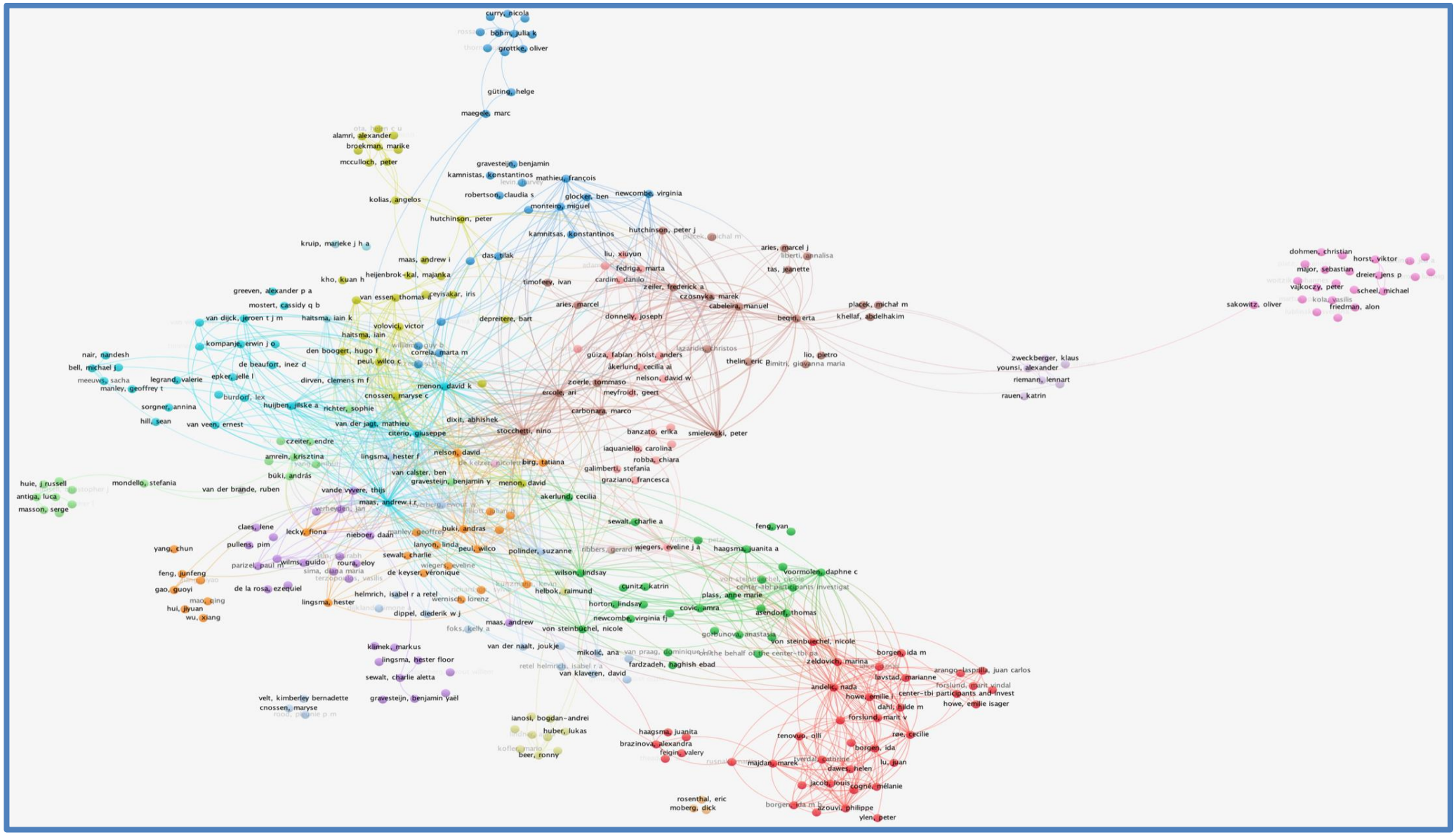

Figure 16: Connection map between CENTER-TBI Investigators by publications.

1.5 Public website and contact details

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2 Use and dissemination of foreground

2.1 Dissemination measures, including any scientific publications relating to foreground

Dissemination aimed for widespread knowledge and use of research results by the target population e.g. policy makers, health care professionals and patients. Approaches included publications in the scientific literature, presentations and interactions with policymakers, press releases and media communications, social media accounts, and interactions through the CENTER-TBI website. The publication of our Commissioned Issue on TBI in the Lancet Neurology (see also section 1.3.1) had a direct focus to inform policymakers on the huge burden posed by TBI to society, and was presented at the European Parliament on Nov 7, 2019. In the UK, awareness for TBI at the policy level were realized through the efforts of Prof David Menon in the All-Party Parliamentary Group on Acquired Brain Injury ((https://www.euronews.com/2019/02/25/i-was-not-who-i-was-researcher-into-new-care-for-traumatic-brain-injury-victims).

CENTER-TBI actively sought media attention by various initiatives. Press releases were broadly distributed around the presentation of the Lancet Neurology Commission at the European Parliament and the occasion summarized in a video (https://www.youtube.com/watch?v=VsUk_Q7qnWg). Forbes magazine featured the findings (https://www.forbes.com/sites/nicolefisher/2017/11/09/special-lancet-neurology-issue-targets-political-forum-to-combat-global-tbi/#59d4fd8675a8). CENTER-TBI attracted media interest across the globe, including Australia, China, Belgium, Germany, Hungary, Italy, the Netherlands, and the UK. EuroNews broadcast a special feature on CENTER-TBI in November 2019 (https://www.euronews.com/2019/02/25/i-was-not-who-i-was-researcher-into-new-care-for-traumatic-brain-injury-victims). CENTER-TBI is present in Twitter (@CenterTBI) to inform the lay audience about the importance of TBI prevention and the results of the project. The interest generated is widely diffused across the world showing that dissemination of our results exceeds the European boundaries. An interactive public information platform was implemented on the public section of the CENTER-TBI website (https://www.center-tbi.eu/), that explains the impact and future developments of TBI research in lay language. Via this platform frequent patient requests were received and answered about disease characteristics, rehabilitation possibilities and referrals to TBI specialists worldwide.

The scientific output generated from CENTER-TBI amounts to date to over 200 publications. Details are provided in section 1.3.11, and a full listing is presented below.

2.1.1 List of all scientific (peer reviewed) publications relating to the foreground of the project

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
1	**Collaborative European NeuroTrauma Effectiveness research in TBI (CENTER-TBI): A prospective longitudinal observational study**	Andrew Maas	Neurosurgery	Volume 76(1), January 2015, p 67–80	Wolters Kluwer Health, Inc.		01/01/2015		10.1227/NEU.0000000000000575	Yes
2	**A rally for traumatic brain injury research**	The Lancet Neurology Ed.	The Lancet Neurology	1 December 2013; 12:1127			December 2013		DOI: 10.1016/S1474-4422(13)70266-7	No
3	**Advancing the care for traumatic brain injury: summary results from the IMPACT studies and perspectives on future research**	Maas AIR	The Lancet Neurology	Volume 12, No. 12, p1200–1210, December 2013			17/10/2013		pii: S1474-4422(13)70234-5. 10.1016/S1474-4422(13)70234-5. [Epub ahead of print]	No
4	**Glial fibrillary acidic protein: from intermediate filament assembly and gliosis to neurobiomarker**	Zhihui Yang	Trends Neurosci	2015 Jun; 38(6): 364-374	Cell press		June 2015		http://dx.doi.org/10.1016/j.tins.2015.04.003	No
5	**The Stroke-Migraine Depolarization Continuum**	Dreier JP	Neuron	Volume 86, Issue 4, 20 May 2015, Pages 902–922	Cell press		20 May 2015		10.1016/j.neuron.2015.04.004.	No
6	**A new approach to evidence synthesis in traumatic brain injury: Living systematic reviews**	Anneliese Synnot	J Neurotrauma	2015 Sep 28, Epub ahead of print	Mary Ann Liebert, Inc.		25/08/2016		doi:10.1089/neu.2015.4124	Yes
7	**Epidemiology of traumatic brain injury in Europe**	Wouter Peeters	Acta Neurochirurgica	2015 Oct;157(10):1683-96.	Springer Link		14/08/2015		doi:10.1007/s00701-015-2512-7	Yes
8	**Developing a molecular taxonomy for traumatic brain injury: a perspective to enable the development of diagnostics and therapeutics.**	Jeromin A,	Biomarkers in Medicine	2015;9(7):619-21.	Future Medicine				doi: 10.2217/bmm.15.22	Yes

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
9	**Traumatic brain injury in 2014. Progress, failures and new approaches for TBI research**	Menon DK	Nature Reviews Neurology	2015 Feb;11(2):71-2	Macmillan Publishers Limited, part of Springer Nature		13/01/2015		doi: 10.1038/nrneurol.2014.261	No
10	**The reliability of the Glasgow Coma Scale: a systematic review**	Reith FC,	Intensive Care Medicine	2016 Jan;42(1):3-15	Springer Link		12/11/2015		doi:10.1007/s00134-015-4124-3	No
11	**Adherence to guidelines in adult patients with traumatic brain injury: A living systematic review**	Cnossen MC,	Journal of Neurotrauma	2016 Aug 25	Mary Ann Liebert, Inc.				10.1089/neu.2015.4121	No
12	**Estimating treatment effectiveness of intracranial pressure monitoring in traumatic brain injury**	Cnossen MC	Critical Care Medicine	2015 August 24	Wolters Kluwer Health, Inc.				10.1097/CCM.0000000000001292	No
13	**Epidemiology of traumatic brain injury in Europe: a living systematic review.**	Alexandra Brazinova	Journal of Neurotrauma	2015 Nov 5. [Epub ahead of print]	Mary Ann Liebert, Inc.				doi: 10.1089/neu.2015.4126.	
14	**Assessment of Health-Related Quality of Life after TBI: Comparison of a Disease-Specific (QOLIBRI) with aGeneric (SF-36) Instrument.**	Nicole von Steinbuechel	Behav Neurol. 2016	2016:7928014	Hindawi Publishing Corporation		01/02/2016		doi: 10.1155/2016/7928014	
15	**TBI-the most complex disease in the most complex organ: the CENTER-TBI trial-a commentary.**	Wheble JL	J R Army Med Corps	2016 Apr;162(2):87-9	BMJ Publishing Group Ltd		06/07/2015		doi: 10.1136/jramc-2015-000472.	No
16	**Prevalence of and Risk Factors for Anxiety and Depressive Disorders after Traumatic Brain Injury: A Systematic Review.**	Scholten AC	Journal of Neurotrauma	2016 Apr 29. [Epub ahead of print]	Mary Ann Liebert, Inc.		29/04/2016		10.1089/neu.2015.4252	No
17	**Methods for Prediction Research in Mild Traumatic Brain Injury.**	Cnossen MC	Journal of Neurotrauma	2016 Jun 15 [Epub ahead of print]	Mary Ann Liebert, Inc.		15/06/2016		10.1089/neu.2015.4359.	No

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
18	**Cerebral Perfusion Pressure Targets Individualized to Pressure-Reactivity Index in Moderate to Severe Traumatic Brain Injury: A Systematic Review.**	Needham E	Journal of Neurotrauma	2016 Jun 27. [Epub ahead of print]	Mary Ann Liebert, Inc.		27/06/2016		10.1089/neu.2016.4450	No
19	**Interpreting Quality of Life after Brain Injury Scores: Cross-Walk with the Short Form-36.**	Wilson Lindsay	Journal of Neurotrauma	2016 Jul 8. [Epub ahead of print]	Mary Ann Liebert, Inc.		08/07/2016		10.1089/neu.2015.4287	No
20	**Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands.**	van Essen TA,	Journal of Neurotrauma	2016 Aug 2. [Epub ahead of print]	Mary Ann Liebert, Inc.		02/08/2016		10.1089/neu.2016.4495	No
21	**A State-of-the-Science overview of randomized controlled trials evaluating acute management of moderate to severe TBI**	Bragge P	Journal of Neurotrauma	2016 Aug 15;33(16):1461-78 Epub 2016 Mar 18	Mary Ann Liebert, Inc.		18/03/2016		doi: 10.1089/neu.2015.4233.	No
22	**Variation in Structure and Process of Care in Traumatic Brain Injury: Provider Profiles of European Neurotrauma Centers Participating in the CENTER-TBI Study.**	Cnossen MC	PLoS One	2016 Aug 29;11(8):e0161367	*Public Library of Science* (PLOS)		29/08/2016		doi: 10.1371/journal.pone.0161367. eCollection 2016.	Yes
23	**Continuous EEG Monitoring in Aneurysmal Subarachnoid Hemorrhage: A Systematic Review**	Daniel Kondziella	Neurocritical Care	Vol. 22/Issue 3	*Humana Press*	United States	01/06/2015	450-461	10.1007/s12028-014-0068-7	No
24	**Evidence for Acute Electrophysiological and Cognitive Changes Following Routine Soccer Heading**	Thomas G. Di Virgilio	EBioMedicine	Online publication	*Elsevier*	United States	01/10/2016	N/A	http://dx.doi.org/10.1016/j.ebiom.2016.10.029	Yes
25	**Integrated approaches to paediatric neurocritical care in traumatic brain injury.**	Maas AI	The Lancet Neurology	Volume 12(1)	Elsevier		31/01/2013	26-28	10.1016/S1474-4422(12)70272-7	No
26	**Toward an international initiative for traumatic brain injury research.**	Tosetti P	Journal of Neurotrauma	Volume 30 (issue 14)	Mary Ann Liebert, Inc.		11/07/2013	1211-22	10.1089/neu.2013.2896	No

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
27	**Traumatic brain injury: an international knowledge-based approach.**	Manley GT	JAMA	Volume 310(5)			07/08/2013	473-4	10.1001/jama.2013.169158	No
28	**The impact of previous traumatic brain injury on health and functioning: a TRACK-TBI study.**	Dams-O'Connor K	Journal of Neurotrauma	Volume 30 (issue 24)	Mary Ann Liebert, Inc.		23/10/2013	2014-20	10.1089/neu.2013.3049	No
29	**Death ascertainment and mortality reporting procedure in EU assessed within CENTER-TBI project**	A Brazinova	European Journal of Public Health	Vol. 26/Issue suppl_1	Oxford University Press	United Kingdom	01/11/2016			No
30	**Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis**	Majdan M	The Lancet Public Health	Volume 1, Issue 2, December 2016	Elsevier		01/12/2016	76-83	10.1016/S2468-2667(16)30017-2	Yes
31	**Causes and Consequences of Treatment Variation in Moderate and Severe Traumatic Brain Injury: A Multicenter Study.**	Cnossen MC	Critical Care Medicine	Volume 45(4)	Wolters Kluwer Health, Inc.		01/04/2017	660-669	10.1097/CCM.0000000000002263	No
32	**Efficient Multi-Scale 3D CNN with Fully Connected CRF for Accurate Brain Lesion Segmentation**	K Kamnitsas	Medical Image Analysis	Volume 36	Elsevier		29/10/2016	61-78	https://doi.org/10.1016/j.media.2016.10.004	Yes
33	**Autoimmunity and Traumatic Brain Injury.**	Yang Z	Curr Phys Med Rehabil Rep.	in press	Springer	USA	01/03/2017	in press	10.1007/s40141-017-0146-9	No
34	**Rehabilitation after traumatic brain injury: A survey in 70 European neurotrauma centres participating in the CENTER-TBI study.**	Cnossen MC	Journal of Rehabilitation Medicine	Vol 49, Issue 5	Foundation for Rehabilitation Information		16/05/2017	395-401	10.2340/16501977-2216	Yes
35	**Unsupervised domain adaptation in brain lesion segmentation with adversarial networks**	K. Kamnitsas	Information Processing in Medical Imaging		Springer LNCS		23/05/2017		10.1007/978-3-319-59050-9_47	No
36	**Severe traumatic brain injury: targeted management in the intensive care unit.**	Stocchetti N	The Lancet Neurology	Volume 16(6)	Elsevier	Europe	16/06/2017	452-464	10.1016/S1474-4422(17)30118-7	Yes

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
37	**Factors Influencing the Reliability of the Glasgow Coma Scale: A Systematic Review.**	Reith FC	Neurosurgery	Volume 80, Issue 6	Lippincott Williams and Wilkins		01/06/2017	829-839	10.1093/neuros/nyw178	No
38	**Predictors of Major Depression and Posttraumatic Stress Disorder Following Traumatic Brain Injury: A Systematic Review and Meta-Analysis.**	Cnossen MC	J Neuropsychiatry Clin Neurosci.	2017 Summer;29 (3)	American Psychiatric Publishing Inc.	United States	01/07/2017	206-224	10.1176/appi.neuropsych.16090165	Yes
39	**Health professionals' perception on the traumatic brain injury care pathways: A SWOT Analysis.**	Nada Andelic	Brain Injury	2017;31(6-7):719-1017	Mary Ann Liebert, Inc.		05/07/2017		10.1080/02699052.2017.1312145	No
40	**Years of life lost due to traumatic brain injury in Europe: A cross-sectional analysis of 16 countries.**	Majdan M	PloS Medicine	Online publication	Public Library of Science (PLOS)		11/07/2017		10.1371/journal.pmed.1002331	Yes
41	**Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management.**	Maegele M	The Lancet Neurology	Volume 16(8)	Elsevier		11/07/2017	630-647	10.1016/S1474-4422(17)30197-7	Yes
42	**Management of mild traumatic brain injury at the emergency department and hospital admission in Europe: A survey of 71 neurotrauma centers participating in the CENTER-TBI study.**	Foks KA	Journal of Neurotrauma	Vol. 34/Issue 17	Mary Ann Liebert, Inc.		01/09/2017		10.1089/neu.2016.4919	No
43	**Comparing Plasma Phospho-Tau, Total-Tau and Phospho-Tau/Total Tau Ratio as Acute and Chronic Traumatic Brain Injury Biomarkers.**	Rubenstein, R	JAMA Neurology	Vol. 74(9)	American Medical Association	USA	01/09/2017	1063-1072	10.1001/jamaneurol.2017.0655. PMID: 28738126	Yes
44	**Paroxysmal sympathetic hyperactivity: the storm after acute brain injury.**	Meyfroidt G	The Lancet Neurology	Volume 16(9)	Elsevier		16/09/2017	721-729	10.1016/S1474-4422(17)30259-4	Yes
45	**The chronic and evolving neurological consequences of traumatic brain injury.**	Wilson, L.	The Lancet Neurology	Vol 16 / Issue 10	Elsevier	UK	01/10/2017	813-825	10.1016/S1474-4422(17)30279-X	Yes

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
46	**Variation in blood transfusion and coagulation management in Traumatic Brain Injury at the Intensive Care Unit: A survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study.**	Huijben JA	Journal of Neurotrauma	Epub ahead of print	Mary Ann Liebert, Inc.		21/08/2017	N/A	10.1089/neu.2017.5194	No
47	**Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: A survey in 66 neurotrauma centers participating in the CENTER-TBI study.**	Cnossen, M. C	Critical Care	Volume 21 (1)	Biomed Central		06/09/2017	N/A	10.1186/s13054-017-1816-9	Yes
48	**A systematic review of cerebral microdialysis and outcomes in TBI: relationships to patient functional outcome, neurophysiologic measures, and tissue outcome**	Frederick A. Zeiler	Acta Neurochirurgica	Vol. 159/Issue 12	Springer Link		01/12/2017	2245-2273	10.1007/s00701-017-3338-2	Yes
49	**Continuous Autoregulatory Indices Derived from Multi-Modal Monitoring: Each One is Not Like the Other**	Frederick Zeiler	Journal of Neurotrauma	Volume 34	Mary Ann Liebert		01/06/2017	1-11	10.1089/neu.2017.5129	Yes
50	**Serial Sampling of Serum Protein Biomarkers for Monitoring Human Traumatic Brain Injury Dynamics: A Systematic Review**	Eric Thelin	Frontiers in Neurology	Volume 8/Article 300	Frontiers Media		42919	N/A	10.3389/fneur.2017.00300	Yes
51	**Cerebrospinal Fluid and Microdialysis Cytokines in Severe Traumatic Brain Injury: A Scoping Systematic Review**	Frederick Zeiler	Frontiers in Neurology	Volume 8/Article 331	Frontiers Media		42926	N/A	10.3389/fneur.2017.00331	Yes
52	**Living systematic review: 1. Introduction-the why, what, when, and how.**	Elliott JH	Journal of Clinical Epidemiology	2017 Nov;91:23-30	Elsevier		01/11/2017	23-30	10.1016/j.jclinepi.2017.08.010	Yes
53	**Living systematic reviews: 4. Living guideline recommendations**	Akl EA	Journal of Clinical Epidemiology	2017 Nov;91:47-53	Elsevier		01/11/2017	47-53	10.1016/j.jclinepi.2017.08.009	No

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
54	**Lancet Neurology Commission on TBI. Presented at European Parliament**	Maas A.	Lancet Neurology, The	December 2017. Volume 12, No 4.	Lancet Publishing Group		06/11/2017	20		Yes
55	**Decision making in very severe traumatic brain injury (Glasgow Coma Scale 3-5): a literature review of acute neurosurgical management.**	van Dijck JT	Journal of Neurosurgical Sciences	Apr;62(2)	Minerva Medica	Epub	10/11/2017	153-177	10.23736/S0390-5616.17.04255-2	No
56	**The CENTER-TBI core study: The making-of**	Adrian Burton	Lancet Neurology, The	Vol. 16/Issue 12	Lancet Publishing Group	United Kingdom	01/12/2017	958-959	10.1016/S1474-4422(17)30358-7	No
57	**Pressure Autoregulation Measurement Techniques in Adult TBI, Part I: A Scoping Review of Intermittent/Semi-Intermittent Methods**	Frederick Zeiler	Journal of Neurotrauma	Volume 34/Issue 23	Mary Ann Liebert		01/12/2017	3207-3223	10.1089/neu.2017.5085	Yes
58	**Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research**	Maas AIR	Lancet Neurology	Volume 16, Issue 12	Elsevier		01/12/2017	987-1048	10.1016/S1474-4422(17)30371-X	Yes
59	**Collaborative targeted maximum likelihood estimation for variable importance measure: Illustration for functional outcome prediction in mild traumatic brain injuries.**	Pirracchio R	Statistical Merthods in medical Research	2018 Jan;27(1)	Sage Journals		01/01/2018	286-297	10.1177/0962280215627335	No
60	**Transcranial Doppler Systolic Flow Index and ICP-Derived Cerebrovascular Reactivity Indices in Traumatic Brain Injury**	Frederick Zeiler	Journal of Neurotrauma	Volume 35/Issue 2	Mary Ann Liebert		15/01/2018	314-322	10.1089/neu.2017.5364	Yes
61	**Ensembles of Multiple Models and Architectures for Robust Brain Tumour Segmentation**	Kamnitsas K	International MICCAI Brainlesion Workshop		Springer, Cham	Athens, Greece	17/02/2018	450-462	10.1007/978-3-319-75238-9_38	Yes
62	**Utility-Weighted Modified Rankin Scale as Primary Outcome in Stroke Trials: A Simulation Study.**	Dijkland SA	Stroke	2018 Apr;49(4):965-971	AHA Journals		13/03/2018	965-971	10.1161/STROKEAHA.117.020194.	Yes

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63	**Emergency department overcrowding: a survey among European neurotrauma centres**	Velt KB.	Emergency Medicine Journal	2018;35:447–448	BMJ Journals		21/03/2018	447-449	10.1136/emermed-2017-206796	No
64	**Outcome assessment after traumatic brain injury – Authors' reply**	Lindsay Wilson	Lancet Neurology	Volume 17, Issue 4	Elsevier		01/04/2018	299-300	10.1016/S1474-4422(18)30045-0	No
65	**Neurochirurgische dilemma's bij traumatisch hersenletsel**	T.A. van Essen	TNN Neurochirurgie	46	Ariez Medical Publishing		01/04/2018	N/A	N/A	No
66	**Unsupervised Lesion Detection in Brain CT using Bayesian Convolutional Autoencoders**	Pawlowski N	International Conference on Medical Imaging with Deep Learning			Amsterdam, the Netherlands	11/04/2018			yes
67	**Variation in general supportive and preventive intensive care management of traumatic brain injury: a survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study.**	Huijben JA	Critical Care	2018 Apr 13;22(1):90	Biomed Central		13/04/2018		10.1186/s13054-018-2000-6	Yes
68	**Critical Thresholds of ICP Derived Continous Cerebrovascular Reactivity for Outcome Prediction in Non-Craniectomized TBI Patients: PRx, Pax and RAC**	Frederick Zeiler	Journal of Neurotrauma	Volume 35/Issue 10	Mary Ann Liebert		15/05/2018	1107-1115	10.1089/neu.2017.5472	Yes
69	**Will the Eu Data Protection Regulation 2016/679 Inhibit Critical Care Research?**	Timmers M	Medical Law Review	Epub ahead of print	Oxford Academic		17/05/2018		10.1093/medlaw/fwy023	No
70	**Divergent Classification Methods of Post-Concussion Syndrome after Mild Traumatic Brain Injury: Prevalence Rates, Risk Factors and Functional Outcome.**	Voormolen DC	Journal of Neurotrauma		Mary Ann Liebert, Inc.		01/06/2018		10.1089/neu.2017.5257	Yes

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71	**Traumatic Brain Injury: patient experience and satisfaction with discharge from trauma hospital**	Tverdal C	J Rehab Medicine	Vol 50 issue 6	Foundation for Rehabilitation Information		15/06/2018	505-513	10.2340/16501977-2332	Yes
72	**The currency, completeness and quality of systematic reviews of acute management of moderate to severe traumatic brain injury: A comprehensive evidence map.**	Synnot A	PLOS One	2018 Jun 21;13(6):e0198676			21/06/2018	e0198676	10.1371/journal.pone.0198676	Yes
73	**Effective rehabilitation services in the post-acute phase of moderate and severe traumatic brain injury**	Røe C	Annals of Physical and Rehabilitation Medicine	Vol. 61/July	Elsevier	UK	01/07/2018	e233	10.1016/j.rehab.2018.05.539	Yes
74	**Raising awareness for spinal cord injury research**	Schwab JM	The Lancet Neurology	2018 Jul;17(7):581-582	Elsevier		01/07/2018	581-582	10.1016/S1474-4422(18)30206-0	Yes
75	**Blood-Based Protein Biomarkers for the Management of Traumatic Brain Injuries in Adults Presenting to Emergency Departments with Mild Brain Injury: A Living Systematic Review and Meta-Analysis.**	Mondello S	Journal of Neurotrauma	Epub ahead of print	Mary Ann Liebert, Inc.		02/07/2018	N/A	10.1089/neu.2017.5182	No
76	**Estimating Pressure Reactivity Index Using Non-Invasive Doppler Based Systolic Flow Index**	Frederick Zeiler	Journal of Neurotrauma	Volume 35/Issue 14	Mary Ann Liebert		15/07/2018	1559-1568	10.1089/neu.2017.5596	Yes
77	**Intra- and Extra-Cranial Injury Burden as Drivers of Impaired Cerebrovascular Reactivity in Traumatic Brain Injury**	Frederick Zeiler	Journal of Neurotrauma	Volume 35/Issue 14	Mary Ann Liebert		15/07/2018	1569-1577	10.1089/neu.2017.5595	Yes
78	**Adjusting for Confounding by Indication in Observational Studies: A Case Study in Traumatic Brain Injury**	Cnossen MC	Clinical Epidemiology	Volume 10	Dove Medical Press		18/07/2018	841-852	10.2147/CLEP.S154500	Yes

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79	**Prehospital Trauma Care among 68 European Neurotrauma Centers: Results of the CENTER-TBI Provider Profiling Questionnaires.**	Cnossen MC	Journal of Neurotrauma	Epub ahead of print	Mary Ann Liebert, Inc.		24/07/2018		10.1089/neu.2018.5712	No
80	**Living systematic reviews: A novel approach to create a living evidence base**	Andrew Maas	Journal of Neurotrauma	Epub ahead of print	Mary Ann Liebert, Inc.		04/08/2018	N/A		No
81	**Genetic Influences on Patient Orientated Outcomes in TBI: A Living Systematic Review of Non-APOE Single Nucleotide Polymorphisms**	Frederick Zeiler	Journal of Neurotrauma	Epub ahead of print	Mary Ann Liebert, Inc.		10/08/2018	N/A	10.1089/neu.2017.5583	Yes
82	**Randomized Controlled Trials in Adult Traumatic Brain Injury: A Systematic Review on the Use and Reporting of Clinical Outcome Assessments**	Lindsay Horton	Journal of Neurotrauma	Vol. 35/Issue 17	Mary Ann Liebert, Inc.		01/09/2018	2005-2014	10.1089/neu.2018.5648	No
83	**Central versus Local Radiological Reading of Acute CT Characteristics in Multicentre Traumatic Brain Injury Research.**	Vande Vyvere, Wilms	Journal of Neurotrauma	Epub ahead of print	Mary Ann Liebert, Inc.		27/09/2018		10.1089/neu.2018.6061	No
84	**Comparative Effectiveness of Surgery for Traumatic Acute Subdural Hematoma in an Aging Population.**	van Essen TA	Journal of Neurotrauma	Epub ahead of print	Mary Ann Liebert, Inc.		17/10/2018		10.1089/neu.2018.5869	No
85	**Prediction of Persistent Post-Concussion Symptoms following mild traumatic Brain injury.**	Cnossen MC	Journal of Neurotrauma	Vol. 35/Issue 22	Mary Ann Liebert, Inc.	United States	15/11/2018	2691-2698	10.1089/neu.2017.5486.	Yes
86	**Terminal spreading depolarizations cause electrocortical silencing prior to clinical brain death**	Andrew P. Carlson	Journal of Neurosurgery	Dec	American Association of Neurological Surgeons		07/12/2018	1–7	10.3171/2018.7.JNS181478	No
87	**Early focal brain injury after subarachnoid hemorrhage correlates with spreading depolarizations**	Nina Eriksen	Neurology	Vol. 92/Issue 4	Lippincott Williams and Wilkins		22/01/2019	e326-e341	dx.doi.org/10.1212/WNL.0000000000006814	No

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88	**Medical Device Connectivity Challenges Outline the Technical Requirements and Standards For Promoting Big Data Research and Personalized Medicine in Neurocritical Care.**	Rodriguez A	Military Medicine	Volume 183, Issue suppl_1, March-April 2018	Oxford Academic		03/04/2018	99–104	10.1093/milmed/usx146	Yes
89	**What happens inside an injured brain?**	Anthony King	Horizon: the EU Research & Innovation magazine; 14 September 2018				14/09/2018			Yes
90	**Intensive care admission criteria for traumatic brain injury patients across Europe.**	Volovici V	Journal of Critical Care	Volume 49, February 2019	Elsevier		08/11/2018	158-161	10.1016/j.jcrc.2018.11.002	No
91	**A case report of delayed cortical infarction adjacent to sulcal clots after traumatic subarachnoid hemorrhage in the absence of proximal vasospasm**	Schinke C	BMC Neurology	Vol. 18/Issue 1	BioMed Central	United Kingdom	01/12/2018	210	10.1186/s12883-018-1217-y	Yes
92	**Brain death and postmortem organ donation: report of a questionnaire from the CENTER-TBI study.**	van Veen E	Critical Care	Vol. 22/Issue 1	BioMed Central	United Kingdom	01/12/2018		10.1186/s13054-018-2241-4	Yes
93	**The association between post-concussion symptoms and health-related quality of life in patients with mild traumatic brain injury.**	Voormolen DC	Injury	Vol. 50/Issue 5	Elsevier	United Kingdom	07/12/2018		10.1016/j.injury.2018.12.002	No
94	**A Multidimensional Approach to Post-concussion Symptoms in Mild Traumatic Brain Injury.**	Polinder S	Frontiers in Neurology	Vol. 9	Frontiers Media	United States	19/12/2018		10.3389/fneur.2018.01113	Yes
95	**The patient with severe traumatic brain injury: clinical decision-making: the first 60 min and beyond**	Jeroen T J M van Dijck	Current Opinion in Critical Care	Volume 25 - issue 6	Lippincott Williams and Wilkins	UK	01/01/2019	622-629	10.1097/MCC.0000000000000671	No
96	**Na+/K+-ATPase α isoform deficiency results in distinct spreading depolarization phenotypes**	Reiffurth C	Journal of Cerebral Blood	in press	Nature Publishing Group	United Kingdom	28/02/2019	in press	10.1177/0271678X19833757	Yes

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			Flow and Metabolism							
97	**Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study.**	van Essen TA	Acta Neurochirurgica	March 2019, Volume 161, Issue 3	Springer Wien	Austria	01/03/2019	435–449	10.1007/s00701-018-3761-z	Yes
98	**Ventricular Drainage Catheters versus Intracranial Parenchymal Catheters for Intracranial Pressure Monitoring-Based Management of Traumatic Brain Injury: A Systematic Review and Meta-Analysis.**	Volovici V	J Neurotrauma	2019 Apr 1;36(7)	Mary Ann Liebert Inc	United States	01/04/2019	988-995	10.1089/neu.2018.6086	Yes
99	**Potential of a statistical approach for the standardization of multicenter diffusion tensor data: A phantom study.**	Timmermans C	Journal of Magnetic Resonance Imaging	Vol. 49/Issue 4	John Wiley and Sons Inc.	United States	01/04/2019	955-965	10.1002/jmri.26333	No
100	**Prevalence of post-concussion-like symptoms in the general population in Italy, The Netherlands and the United Kingdom.**	Voormolen DC	Brain Injury	Volume 33, 2019 - Issue 8	Informa Healthcare	United Kingdom	19/04/2019	1078-1086	10.1080/02699052.2019.1607557	Yes
101	**Location of traumatic brain injury-related deaths: epidemiological analysis of 11 Europeancountries**	Zelinkova V	Brain Injury	Volume 33, 2019 - Issue 7	Taylor & Francis		21/04/2019	830-835	10.1080/02699052.2019.1605622	No
102	**Protocolised thromboelastometric-guided haemostatic management in patients with traumatic brain injury: a pilot study**	Gratz J	Anaesthesia	Epub ahead of print Volume 74, Issue7, July 2019	Wiley		29/04/2019	883-890	10.1111/anae.14670	No
103	**Early blood-brain barrier dysfunction predicts neurological outcome following aneurysmal subarachnoid hemorrhage**	Lublinsky S	EBioMedicine	Vol 43	Elsevier	United States	01/05/2019	460-472	10.1016/j.ebiom.2019.04.054	Yes
104	**Variation in Guideline Implementation and Adherence Regarding Severe Traumatic Brain Injury Treatment: A CENTER-TBI Survey Study in Europe.**	Volovici V	World Neurosurgery	Vol. 125	Elsevier Inc.	United States	01/05/2019	e515-e520	10.1016/j.wneu.2019.01.116	Yes

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105	**Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma (t-ASDH): a neurosurgical paradox?**	van Dijck JTJM	Acta Neurochirurgica	Vol. 161/Issue 5	Springer Wien	Austria	01/05/2019	875-884	10.1007/s00701-019-03878-5	yes
106	**Development of a Minimum Reporting Set for Rehabilitation Interventions Based on ICSO-R**	Røe C	Brain Injury	Vol. 33/Issue sup1	Taylor Francis online		02/05/2019		10.1080/02699052.2019.1608749	no
107	**Pediatric Traumatic Brain Injury: Neurocognitive and Psychosocial Outcome 6 Months Post-Injury**	Holthe IM	Brain Injury	Vol. 33/Issue sup1	Taylor Francis online		02/05/2019		10.1080/02699052.2019.1608749	no
108	**In-hospital costs after severe traumatic brain injury: A systematic review and quality assessment.**	van Dijck JTJM et al.	PLOS ONE	Vol. 14/ Issue 5	PLOS ONE	PLOS ONE	09/05/2019	e0216743	10.1371/journal.pone.0216743	Yes
109	**Comparison of Performance of Different Optimal Cerebral Perfusion Pressure Parameters for Outcome Prediction in Adult Traumatic Brain Injury: A Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Study.**	Zeiler FA	Journal of Neurotrauma	Vol. 36/Issue 10	Mary Ann Liebert Inc	United States	15/05/2019	1505-1517	10.1089/neu.2018.6182	Yes
110	**Automatic Quantification of Computed Tomography Features in Acute Traumatic Brain Injury.**	Jain S	Journal of Neurotrauma	Vol. 36, No. 11	Mary Ann Liebert Inc	United States	01/06/2019		10.1089/neu.2018.6183	No
111	**Univariate comparison of performance of different cerebrovascular reactivity indices for outcome association in adult TBI: a CENTER-TBI study.**	Zeiler FA	Acta Neurochir (Wien). 2019 Jun;161(6):1217-1227. doi: . Epub 2019 Mar 15.	June 2019, Volume 161, Issue 6	Springer Wien	Austria	01/06/2019	pp 1217–1227	10.1007/s00701-019-03844-1	Yes
112	**Neurostereologic lesion volumes and spreading depolarizations in severe traumatic brain injury patients: a pilot study**	Eriksen N	Neurocritical Care	Vol 30/Issue 3	Humana Press	United States	01/06/2019	557-568	10.1007/s12028-019-00692-w	No

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113	**Randomized Controlled Trials of Rehabilitation Services in the Post-acute Phase of Moderate and Severe Traumatic Brain Injury - A Systematic Review**	Røe C	Front Neurol.		Frontiers Media		06/06/2019		10.3389/fneur.2019.00557	yes
114	**Patient-specific ICP Epidemiologic Thresholds in Adult Traumatic Brain Injury: A CENTER-TBI Validation Study.**	Zeiler FA	Journal of Neurosurgical Anesthesiology	Epub ahead of print	Lippincott Williams and Wilkins	United States	18/06/2019	1	10.1097/ANA.0000000000000616	No
115	**Cerebrovascular reactivity is not associated with therapeutic intensity in adult traumatic brain injury: a CENTER-TBI analysis.**	Zeiler FA	Acta Neurochirurgica	Epub ahead of print	Springer Wien	Austria	25/06/2019	1955-1964	10.1007/s00701-019-03980-8	Yes
116	**Spreading depolarizations in the rat endothelin-1 model of focal cerebellar ischemia**	Oliveira-Ferreira AI	Journal of Cerebral Blood Flow and Metabolism	in press	Nature Publishing Group	United Kingdom	07/07/2019	in press	10.1177/0271678X19861604	Yes
117	**Posttraumatic stress disorder after civilian traumatic brain injury: a systematic review and meta-analysis of prevalence rates.**	Van Praag DLG	Journal of Neurotrauma	Epub ahead of print	Mary Ann Liebert		02/08/2019	N/A	10.1089/neu.2018.5759	Yes
118	**Prevalence of near-death experiences in people with and without REM sleep intrusion**	Kondziella D	Peer J	Vol 7	Peer J		27/08/2019	e7585	10.7717/peerj.7585	Yes
119	**Semiology and Mechanisms of Near-Death Experiences**	Peinkhofer C	Current Neurology and Neuroscience Reports	Vol 19/Issue 9	Current Medicine Group	United States	01/09/2019	62	10.1007/s11910-019-0983-2.	No
120	**Variation in the practice of tracheal intubation in Europe after traumatic brain injury: a prospective cohort study.**	Gravesteijn BY	Anaesthesia	Epub ahead of print	Blackwell Publishing	United Kingdom	13/09/2019	N/A	10.1111/anae.14838	Yes
121	**Comparative effectiveness of surgery in traumatic acute subdural and intracerebral haematoma: study**	Van Essen TA	BMJ Open	Vol. 9/Issue 10	BMJ Publishing Group	United Kingdom	01/10/2019	e033513	10.1136/bmjopen-2019-033513.	Yes

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	protocol for a prospective observational study within CENTER-TBI and Net-QuRe.									
122	**Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study.**	Steyerberg EW	Lancet Neurology	Vol. 18/Issue 10	Lancet Publishing Group	United Kingdom	01/10/2019	923-934	10.1016/S1474-4422(19)30232-7	Yes
123	**TBI Lesion Segmentation in Head CT: Impact of Preprocessing and Data Augmentation.**	Miguel Monteiro	MICCAI Brain Lesion Workshop	2019	MICCAI		17/10/2019			Yes
124	**Coagulopathy after hemorrhagic traumatic brain injury, an observational study of the incidence and prognosis**	Jort A.N. van Gent	Acta Neurochirurgica	in press	Springer Wien	Austria	18/11/2019	in press	10.1007/s00701-019-04111-z	Yes
125	**Development of a quality indicator set to measure and improve quality of ICU care for patients with traumatic brain injury**	Jilske A. Huijben	Critical Care	N°23, article number 95	Critical Care	BioMed Central	01/12/2019		10.1186/s13054-019-2377-x	Yes
126	**HDF5-Based Data Format for Archiving Complex Neuro-monitoring Data in Traumatic Brain Injury Patients**	Cabeleira M	Acta Neurochir Suppl.	2018;126; 121-125.			01/03/2018	121-125	10.1007/978-3-319-65798-1_26	No
127	**Traumatic brain injury in China**	Ji-Yao Jiang	The Lancet Neurology,	Volume 18, Issue 3, 2019, ISSN 1474-4422			01/03/2019	Pages 286-295	10.1016/S1474-4422(18)30469-1.	Yes
128	**Factors Associated with Participation in Life Situations for Adults With ABI: A Systematic Review.**	Ezekiel L	Arch Phys Med Rehabil	2019;100			01/05/2019	945-955	10.1016/j.apmr.2018.06.017	Yes
129	**Compensatory-reserve-weighted intracranial pressure versus intracranial pressure for outcome association in adult traumatic brain injury: a CENTER-TBI validation study.**	Zeiler FA	Acta Neurochir (Wien)	2019 Jul;161(7):1275-1284			01/07/2019		10.1007/s00701-019-03915-3.	Yes
130	**Understanding the Consequences of Repetitive Subconcussive Head Impacts in Sport: Brain Changes and Dampened**	Di Virgilio, T.G	Frontiers in Human Neuroscience	13	Frontiers Media		10/09/2019	Article 294	10.3389/fnhum.2019.00294	Yes

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	Motor Control Are Seen After Boxing Practice									
131	**Handling of Missing Outcome Data in Traumatic Brain Injury Research: A Systematic Review.**	Richter S	J Neurotrauma. 2019 Oct 1;36(19)	Vol. 36, No. 19			10/09/2019	2743-2752	10.1089/neu.2018.6216	Yes
132	**The psychometric validation of the Dutch version of the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) after traumatic brain injury (TBI)**	Plass AM	PLoS One	2019 Oct 24; 14(10)	PMC		24/10/2019		10.1371/journal.pone.0210138	Yes
133	**Post-Concussion Symptoms in Complicated vs. Uncomplicated Mild Traumatic Brain Injury Patients at Three and Six Months Post-Injury: Results from the CENTER-TBI Study**	Daphne C. Voormolen	Journal of Clincal Medicine	8(11), 1921	MDPI open access journals		08/11/2019	1921	10.3390/jcm8111921	Yes
134	**Migraine aura, a predictor of near-death experiences in a crowdsourced study.**	Kondziella D	PeerJ		PeerJ		04/12/2019	e8202	10.7717/peerj.8202	Yes
135	**Direct electrophysiological evidence that spreading depolarization-induced spreading depression is the pathophysiological correlate of the migraine aura and a review of the spreading depolarization continuum of acute neuronal mass injury.**	Major S	Geroscience		Geroscience		09/12/2019	42:57-80	10.1007/s11357-019-00142-7	Yes
136	**Lasting s-ketamine block of spreading depolarizations in subarachnoid hemorrhage: a retrospective cohort study.**	Santos E	Crit Care		Crit Care		30/12/2019	23:427	10.1186/s13054-019-2711-3	Yes
137	**Prognosis in moderate and severe traumatic brain injury: a systematic review of contemporary models and validation studies.**	Dijkland, S. A	Journal of neurotrauma	37(1): 1-13. 2020			01/01/2020		10.1089/neu.2019.6401	Yes
138	**Measurement invariance of assessments of depression (PHQ-9) and anxiety (GAD-7) across sex, strata and**	Teymoori A	J Affect Disord.	Volume 262	Elsevier		01/02/2020	278-285	doi: 10.1016/j.jad.2019.10.035	n

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	linguistic backgrounds in a European-wide sample of patients after Traumatic Brain Injury.									
139	**Experiences of fatigue in daily life of people with acquired brain injury: a qualitative study.**	Ezekiel L,	Disabil Rehabil	2020 Feb 4:1-9			04/02/2020	Epub	10.1080/09638288.2020.1720318	Yes
140	**Unmeasured confounding in observational studies of management of cerebellar intracranial hemorrhage**	Van Essen TA	JAMA	2020;323(7):665-666.	American Medical Association		18/02/2020	665	10.1001/jama.2019.20851	yes
141	**Does Complement-Mediated Hemostatic Disturbance Occur in Traumatic Brain Injury? A Literature Review and Observational Study Protocol.**	Fletcher-Sandersjöö A	Int J Mol Sci	Vol. 21/Issue 5			26/02/2020	1596	10.3390/ijms21051596	Yes
142	**Changes in Coagulation following brain injury**	Maegele M	Semi Thromb Hemost	Vol.46/Issue 2	Thieme Medical Publishers	United States	11/03/2020	155-166	10.1055/s-0040-1702178	No
143	**Guidelines for Data Acquisition, Quality & Curation for Observational Research Designs (DAQCORD)**	Ercole, A	Journal of Clinical and Translational Science	4(4)	Cambridge University Press	UK	13/03/2020	354-359	10.1017/cts.2020.24	Yes
144	**Factorial Structure and Validity of Depression (PHQ-9) and Anxiety (GAD-7) Scales after Traumatic Brain Injury.**	Teymoori A	J Clin Med.	2020 23;9(3)	MDPI open access journals		23/03/2020		10.3390/jcm9030873	Yes
145	**Prognostic value of spreading depolarizations in patients with severe traumatic brain injury.**	Hartings JA	JAMA Neurology		JAMA Neurology		01/04/2020	77:489-499	10.1001/jamaneurol.2019.4476	Yes
146	**Biomarkers for Traumatic Brain Injury: Data Standards and Statistical Considerations.**	Huie JR	J Neurotrauma.				01/04/2020	Epub ahead of print.	10.1089/neu.2019.6762	Yes
147	**The role of spreading depolarizations and electrographic seizures in early injury progression of the rat photothrombosis stroke model.**	Schoknecht K	J Cereb Blood Flow Metab		J Cereb Blood Flow Metab		02/04/2020	41:413-430	10.1177/0271678X20915801	Yes

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148	**Toward a New Multi-Dimensional Classification of Traumatic Brain Injury: A Collaborative European NeuroTrauma Effectiveness Research for Traumatic Brain Injury Study**	Gravesteijn, B. Y	Journal of neurotrauma	37(7): 1002-1010.			03/04/2020		10.1089/neu.2019.6764	Yes
149	**Preliminary validation of the Dutch version of the Posttraumatic stress disorder checklist for DSM-5 (PCL-5) after traumatic brain injury in a civilian population**	Van Praag DLG	PLoS One	2020 Apr 20;15(4):e0231857.	PMC		20/04/2020		10.1371/journal.pone.0231857	Yes
150	**Injury Causes and Severity in Pediatric Traumatic Brain Injury Patients Admitted to the Ward or Intensive Care Unit: A Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Study**	Lennart Riemann	Neurotrauma	Volume 11, Article 345	Frontiers in Neurology	-	30/04/2020	-	10.3389/fneur.2020.00345	Yes
151	**Prevalence of visual snow syndrome in the UK.**	Kondziella D	Eur J Neu		Eur J Neu		01/05/2020	27:764-772	10.1111/ene.14150	No
152	**Tracheostomy practice and timing in traumatic brain-injured patients: a CENTER-TBI study**	Chiara Robba	Intensive Care Medicine	volume 46, issue 5	Springer Nature		01/05/2020	983-994	10.1007/s00134-020-05935-5	No
153	**Outcomes after Complicated and Uncomplicated Mild Traumatic Brain Injury at Three-and Six-Months Post-Injury: Results from the CENTER-TBI Study**	Voormolen, D.C.	Journal of Clinical Medicine	2020, 9(5), 1525	MDPI open access journals	Switzerland	01/05/2020	Article 1525	10.3390/jcm9051525	Yes
154	**Changing care pathways and between-center practice variations in intensive care for traumatic brain injury across Europe: a CENTER-TBI analysis.**	Huijben JA	Intensive Care Med.	2020 May;46(5)			04/05/2020	995-1004	10.1007/s00134-020-05965-z	Yes
155	**Association between Cerebrovascular Reactivity Monitoring and Mortality Is Preserved When Adjusting for Baseline Admission Characteristics in Adult**	Zeiler FA	J Neurotrauma.	2020 May 15;37(10):1233-1241.			05/05/2020	1233-1241	10.1089/neu.2019.6808	Yes

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
	Traumatic Brain Injury: A CENTER-TBI Study.									
156	**Harmonization of Brain Diffusion MRI: Concepts and Methods.**	Pinto MS	Front Neurosci.	2020;14:396			06/05/2020		10.3389/fnins.2020.00396	Yes
157	**Multiclass semantic segmentation and quantification of traumatic brain injury lesions on head CT using deep learning: an algorithm development and multicentre validation study**	Miguel Monteiro	The Lancet Digital Health	Volume 2, Issue 6	Elsevier	Online	14/05/2020	e314-e322	10.1016/S2589-7500(20)30085-6	Yes
158	**Differences in Health-Related Quality of Life after Traumatic Brain Injury between varying Patient Groups: Sensitivity of a Disease Specific (QOLIBRI) and a Generic (SF-36) Instrument.**	von Steinbuechel N	J Neurotrauma.	Volume: 37 Issue 10: May 5, 2020	Mary Ann Liebert		15/05/2020	1242-1254.	10.1089/neu.2019.6627	No
159	**Evaluation of the relationship between slow-waves of intracranial pressure, mean arterial pressure and brain tissue oxygen in TBI: a CENTER-TBI exploratory analysis.**	Zeiler FA	J Clin Monit Comput.	2020 May 16.			16/05/2020		10.1007/s10877-020-00527-6	Yes
160	**Prognostic Research in Traumatic Brain Injury: Markers, Modeling, and Methodological Principles.**	Retel Helmrich IRA	J Neurotrauma.	2020 May 20.			20/05/2020	Epub ahead of print.	10.1089/neu.2019.6708	Yes
161	**Prognostic Validation of the NINDS Standardized Pathoanatomic Terms and Definitions for the Reporting of Acute Traumatic Brain Injuries: A CENTER-TBI study.**	Vande Vyvere T	J. Neurotrauma	Epub ahead of print	Mary Ann Liebert		01/06/2020		10.1089/neu.2019.6710	Yes
162	**Common Data Elements - A critical assessment of harmonization between current multicenter traumatic brain injury studies.**	Meeuws S	J. Neurotrauma	Epub ahead of print	Mary Ann Liebert		01/06/2020		10.1089/neu.2019.6867.	Yes
163	**Statistical Cerebrovascular Reactivity Signal Properties after Secondary Decompressive Craniectomy in**	Zeiler FA	J Neurotrauma.	2020 Jun 1;37(11):1306-1314			01/06/2020		10.1089/neu.2019.6726	Yes

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
	Traumatic Brain Injury: A CENTER-TBI Pilot Analysis.									
164	**Blood biomarkers on admission in acute traumatic brain injury: Relations to severity, CT findings and care path in the CENTER-TBI study.**	Czeiter E	EBioMedicine	Volume 56	Elsevier		01/06/2020	102785 (1-11)	10.1016/j.ebiom.2020.102785	Yes
165	**Machine learning algorithms performed no better than regression models for prognostication in traumatic brain injury.**	Gravesteijn, B. Y.	Journal of clinical epidemiology	Volume 122			01/06/2020	95-107	10.1016/j.jclinepi.2020.03.005	Yes
166	**Influence of Sociodemographic, Premorbid, and Injury-Related Factors on Post-Concussion Symptoms after Traumatic Brain Injury**	Zeldovich M	J. Clin. Med	2020, 9(6), 1931	MDPI open access journals		01/06/2020		10.3390/jcm9061931	Yes
167	**Early Predictors of Employment Status One Year Post Injury in Individuals with Traumatic Brain Injury in Europe.**	Arango-Lasprilla JC	J Clin Med	2020 Jun 26;9(6)	MDPI open access journals	Basel, Switzerland	01/06/2020	2007	10.3390/jcm9062007	Yes
168	**Functional outcome, in-hospital healthcare consumption and in-hospital costs for hospitalised traumatic brain injury patients: a Dutch prospective multicentre study**	Jeroen T J M van Dijck	Acta Neurochir (Wien)	Volume 162	Springer Wien	Austria	01/07/2020	1607-1618	10.1007/s00701-020-04384-9	Yes
169	**Relationship between Measures of Cerebrovascular Reactivity and Intracranial Lesion Progression in Acute Traumatic Brain Injury Patients: A CENTER-TBI Study.**	Mathieu F	J Neurotrauma.	2020 Jul 1;37(13):1556-1565			01/07/2020		10.1089/neu.2019.6814.	Yes
170	**Reference Values of the QOLIBRI from General Population Samples in the United Kingdom and The Netherlands.**	Gorbunova A	J. Clin. Med	2020 9(7), 2100	MDPI open access journals		01/07/2020		10.3390/jcm9072100	yes

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
171	**Diffuse Intracranial Injury Patterns Are Associated with Impaired Cerebrovascular Reactivity in Adult Traumatic Brain Injury: A CENTER-TBI Validation Study.**	Zeiler FA	J Neurotrauma	2020 Jul 15;37(14):1597-1608			15/07/2020		10.1089/neu.2019.6959	Yes
172	**Comparison of Care System and Treatment Approaches for Patients with Traumatic Brain Injury in China versus Europe: A CENTER-TBI Survey Study.**	Feng J	J Neurotrauma.	Vol 37, No 16			15/08/2020		10.1089/neu.2019.6900.	Yes
173	**End-of-life practices in traumatic brain injury patients: Report of a questionnaire from the CENTER-TBI study.**	Ernest van Veen	Journal of Critical Care	2020 Aug;58:78-88.			01/08/2020		10.1016/j.jcrc.2020.04.001	Yes
174	**Global traumatic brain injury research enters a new era**	Maegele M	The Lancet Neurology	Vol.19/Issue 8	Elsevier		01/08/2020	637-639	10.1016/S1474-4422(20)30208-8	No
175	**Predictors of Access to Rehabilitation in the Year Following Traumatic Brain Injury: A European Prospective and Multicenter Study.**	Jacob L	Neurorehabilitation and Neural repair	2020 Sep;34(9):814-830	Sage Journals		07/08/2020	814-830	10.1177/1545968320946038	Yes
176	**Brain Tissue Oxygen and Cerebrovascular Reactivity in Traumatic Brain Injury: A Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury Exploratory Analysis of Insult Burden.**	Zeiler FA	J Neurotrauma.	2020 Sep 1;37(17):1854-1863			01/09/2020		10.1089/neu.2020.7024	Yes
177	**Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Investigators and Participants. Impact of Antithrombotic Agents on Radiological Lesion Progression in Acute Traumatic Brain Injury: A CENTER-TBI Propensity-Matched Cohort Analysis.**	Mathieu F	J Neurotrauma. 2020 Oct 1;37(19):	Vol. 37, No. 19			18/09/2020	2069-2080	10.1089/neu.2019.6911	Yes

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
178	**Informed consent procedures in patients with an acute inability to provide informed consent: Policy and practice in the CENTER-TBI study.**	Roel P J van Wijk	Journal of Critical Care	2020 Oct;59:6-15	Elvesier		01/10/2020		10.1016/j.jcrc.2020.05.004	Yes
179	**Prehospital Management of Traumatic Brain Injury across Europe: A CENTER-TBI Study.**	Benjamin Y Gravesteijn	Prehospital emergency care	2020 Oct 1;1-15.	Taylor Francis Online		01/10/2020	1-22.	10.1080/10903127.2020.1817210	Yes
180	**Tracheal intubation in traumatic brain injury: a multicentre prospective observational study.**	Gravesteijn BY	Br J Anaesth.	Vol 125, Issue 4			01/10/2020	505-517	10.1016/j.bja.2020.05.067	Yes
181	**Health-related quality of life after traumatic brain injury: deriving value sets for the QOLIBRI-OS for Italy, The Netherlands and The United Kingdom**	Daphne C Voormolen	Qual Life Res.	29, 3095–3107 (2020)	Springer		01/11/2020	3095–3107	10.1007/s11136-020-02583-6	Yes
182	**Descriptive analysis of low versus elevated intracranial pressure on cerebral physiology in adult traumatic brain injury: a CENTER-TBI exploratory study.**	Frederick A Zeiler	Acta Neurochirurgica	2020 Nov;162(11):2695-2706.			01/11/2020		10.1007/s00701-020-04485-5	Yes
183	**The Effect of Temperature Increases on Brain Tissue Oxygen Tension in Patients with Traumatic Brain Injury: A Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury Substudy.**	Rass V	Ther Hypothermia Temp Manag	2020 Nov 17	Mary Ann Liebert		17/11/2020		10.1089/ther.2020.0027	Yes
184	**Care transitions in the first 6 months following traumatic brain injury: Lessons from the CENTER-TBI study**	Borgen, I	Ann Phys Rehabil Med.	2020;S1877-0657(20)30217-7	Elsevier	Amsterdam, the Netherlands	24/11/2020	Epub ahead of print	10.1016/j.rehab.2020.10.009	Yes
185	**How do 66 European institutional review boards approve one protocol for an international prospective observational study on traumatic brain injury? Experiences from the CENTER-TBI study.**	Timmers M	BMC Med Ethics.	2020 May 12;21(1):36.			01/12/2020		10.1186/s12910-020-00480-8.	Yes

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186	**Low-resolution pressure reactivity index and its derived optimal cerebral perfusion pressure in adult traumatic brain injury: a CENTER-TBI study**	Lennart Riemann	Critical Care	Volume 24, Issue 1		-	01/12/2020	266	10.1186/s13054-020-02974-8	Yes
187	**Incidence, Risk Factors, and Effects on Outcome of Ventilator-Associated Pneumonia in Patients With Traumatic Brain Injury: Analysis of a Large, Multicenter, Prospective, Observational Longitudinal Study.**	Chiara Robba	Chest	Volume 158, Issue 6, December 2020	Elsevier		01/12/2020	2292-2303	10.1016/j.chest.2020.06.064	Yes
188	**Informed consent procedures for emergency interventional research in patients with traumatic brain injury and ischaemic stroke.**	Kompanje EJO	Lancet Neurol.	2020 Dec;19(12)			01/12/2020	1033-1042	10.1016/S1474-4422(20)30276-3.	Yes
189	**Global Characterisation of Coagulopathy in Isolated Traumatic Brain Injury (iTBI): A CENTER-TBI Analysis**	Böhm JK,Güting	Neurocritical Care	in press	Springer		11/12/2020	in press	10.1007/s12028-020-01151-7	Yes
190	**Impact of duration and magnitude of raised intracranial pressure on outcome after severe traumatic brain injury: A CENTER-TBI high-resolution group study.**	Åkerlund CA	PLoS One	2020 Dec 14;15(12):e0243427.			14/12/2020		10.1371/journal.pone.0243427.	Yes
191	**Differences between men and women in treatment and outcome following traumatic brain injury**	Ana Mikolic	J Neurotrauma.		Mary Ann Liebert		31/12/2020		10.1089/neu.2020.7228	Yes
192	**Association between Physiological Signal Complexity and Outcomes in Moderate and Severe Traumatic Brain Injury: A CENTER-TBI Exploratory Analysis of Multi-Scale Entropy.**	Zeiler FA	J Neurotrauma.	2021 Jan 15;38(2):272-282			31/12/2020		10.1089/neu.2020.7249.	Yes
193	**Prediction of global functional outcome and post-concussive symptoms following mild traumatic brain injury:**	Ana Mikolic	J Neurotrauma	Vol 38, No 2	Mary Ann Liebert		31/12/2020		doi: 10.1089/neu.2020.7074	Yes

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	external validation of prognostic models in the CENTER-TBI study									
194	**Analysis of Cardio-Cerebral Crosstalk Events in an Adult Cohort from the CENTER-TBI Study**	Dimitri GM	Acta Neurochir Suppl.	2021;131:39-42.			01/01/2021		10.1007/978-3-030-59436-7_9.	Yes
195	**Automatic Pulse Classification for Artefact Removal Using SAX Strings, a CENTER-TBI Study.**	Cabeleira M	Acta Neurochir Suppl.	2021;131:231-234.			01/01/2021		10.1007/978-3-030-59436-7_44.	Yes
196	**CENTER-TBI High Resolution Substudy Participants and Investigators. Patient's Clinical Presentation and CPPopt Availability: Any Association?**	Liberti A	Acta Neurochir Suppl.	2021;131:167-172			01/01/2021		10.1007/978-3-030-59436-7_34	Yes
197	**DeepClean: Self-Supervised Artefact Rejection for Intensive Care Waveform Data Using Deep Generative Learning.**	Edinburgh T	Intracranial Pressure and Neuromonitoring XVII	2021;131:235-241.			01/01/2021		10.1007/978-3-030-59436-7_45.	Yes
198	**Python-Embedded Plugin Implementation in ICM+: Novel Tools for Neuromonitoring Time Series Analysis with Examples Using CENTER-TBI Datasets.**	Placek MM	Intracranial Pressure and Neuromonitoring XVII	2021;131:255-260			01/01/2021		10.1007/978-3-030-59436-7_48	Yes
199	**Prediction model for intracranial hypertension demonstrates robust performance during external validation on the CENTER-TBI dataset.**	Carra G	Intensive Care Medicine	2021 Jan;47(1):124-126.			01/01/2021		10.1007/s00134-020-06247-4	Yes
200	**Frequency of fatigue and its changes in the first 6 months after traumatic brain injury: results from the CENTER-TBI study.**	Andelic N	J Neurology	2021 Jan;268(1)	Springer Berlin ; New York, Springer-Verlag		01/01/2021	61-73	10.1007/s00415-020-10022-2	Yes
201	**Acute Kidney Injury in Traumatic Brain Injury Patients: Results From the Collaborative European NeuroTrauma**	Chiara Robba	Crit Care Med	volume 49, issue 1	Wolters Kluwer		01/01/2021	112-126	10.1097/CCM.0000000000004673	No

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
	Effectiveness Research in Traumatic Brain Injury Study				Health, Inc.					
202	**Health-related quality of life after pediatric traumatic brain injury: A qualitative comparison between children's and parents' perspectives.**	Krenz U	PLoS One		PMC		10/02/2021		10.1371/journal.pone.0246514	yes
203	**Imputation of Ordinal Outcomes: A Comparison of Approaches in Traumatic Brain Injury**	Kunzmann, K.	Journal of Neurotrauma	38(4)	Mary Ann Liebert Inc	United States	15/02/2021	455-463	10.1089/neu.2019.6858	Yes
204	**Missing Data in Prediction Research: A Five-Step Approach for Multiple Imputation, Illustrated in the CENTER-TBI Study.**	Gravesteijn BY	J Neurotrauma.	Epub ahead of print			25/02/2021	Epub ahead of print	10.1089/neu.2020.7218	Yes
205	**Spreading depolarization evoked by endothelin-1 is inhibited by octanol but not by carbenoxolone.**	Petzold GC	Brain Hemorrhages		Brain Hemorrhages		01/03/2021	2:6-14	https://doi.org/10.1016/j.hest.2020.08.002	Yes
206	**Unmet Rehabilitation Needs after Traumatic Brain Injury across Europe: Results from the CENTER-TBI Study**	Andelic N	Journal of Clinical Medicine	2021 Mar 3;10(5):1035	MDPI AG	Basel, Switzerland	01/03/2021	10(5):1035	10.3390/jcm10051035	Yes
207	**Neuroanatomical Substrates and Symptoms Associated With Magnetic Resonance Imaging of Patients With Mild Traumatic Brain Injury**	Richter S	JAMA Network open	March 18, 2021	American Medical Association		18/03/2021		doi:10.1001/jamanetworkopen.2021.0994	Yes
208	**Systemic Markers of Injury and Injury Response Are Not Associated with Impaired Cerebrovascular Reactivity in Adult Traumatic Brain Injury: A Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Study.**	Zeiler FA	Journal of Neurotrama	2021 Apr 1;38(7):870-878.			01/04/2021		10.1089/neu.2020.7304	Yes
209	**Understanding the relationship between cognitive performance and function in daily life after traumatic brain injury.**	Wilson L	Journal of Neurology, Neurosurgery & Psychiatry	2021;92:407-417.	BMJ Jorunals		01/04/2021	407-417	10.1136/jnnp-2020-324492	Yes

No	Title	Main Author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Date of publication	Relevant pages	Permanent identifiers / doi	Is/Will open access provided to this publication?[2]
210	**Characteristics, management and outcomes of patients with severe traumatic brain injury in Victoria, Australia compared to United Kingdom and Europe: a comparison between two harmonised prospective cohort studies**	Eveline J.A	Injury	2021, ISSN 0020-1383			01/04/2021	ISSN 0020-1383	10.1016/j.injury.2021.04.033	Yes
211	**A Manual for the Glasgow Outcome Scale-Extended (GOSE) Interview**	Wilson, L	Journal of Neurotrauma	Online ahead of print	Mary Ann Liebert Inc	United States	06/04/2021	in press	10.1089/neu.2020.7527	Yes
212	**Persistent postconcussive symptoms in children and adolescents with mild traumatic brain injury receiving initial head computed tomography**	Lennart Riemann	Journal of Neurosurgery: Pediatrics	Online publication before print		-	01/05/2021	Online publication before print	https://doi.org/10.3171/2020.9.PEDS20421	No
213	**Reference Values and Psychometric Properties of the Quality of Life after Traumatic Brain Injury Overall Scale in Italy, the Netherlands, and the United Kingdom**	Yi-Jhen Wu	Value in Health		ISPOR		23/04/2021			No
214	**Outcome Prediction after Moderate and Severe Traumatic Brain Injury: External Validation of Two Established Prognostic Models in 1742 European Patients**	Dijkland SA	J Neurotrauma.	Vol 38, No 10			15/05/2021	Epub ahead of print.	doi: 10.1089/neu.2020.7300.	Yes
215	**Use and impact of high intensity treatments in patients with traumatic brain injury across Europe: a CENTER-TBI analysis**	Huijben, J.A	Critical Care	25, 78.	BMC	UK	01/12/2021	41275	https://doi.org/10.1186/s13054-020-03370-y	Yes
216	**Psychometric Characteristics of the Patient-Reported Outcome Measures Applied in the CENTER-TBI Study**	von Steinbuechel, N	Journal of Clinical Medicine	2021, 10, 2396	MDPI	Switzerland	28/05/2021		10.3390/jcm10112396	Yes

2.1.2 List of all dissemination activities

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
1	Oral presentation to a scientific event	University of Sheffield	CENTER TBI	01/06/2014	Hong Kong Convention Centre	Scientific Community	2,000	International
2	Oral presentation to a scientific event	Ospedale IRCCS Policlinico	Il progetto CENTER – TBI. 22° GIVITI meeting & CREATIVE kick-off meeting	13/11/2013	Pesaro, Italy	Scientific Community	300	International
3	Press releases	Oslo University Hospital (OUS)	Large European study aims to improve treatment for traumatic brain injury	20/10/2013	Oslo	Medias	Unknown	
4	Oral presentation to a wider public	Oslo University Hospital	What is the CENTER-TBI?	09/05/2014	Sunvollen	Clinicians, Scientific community	40	Norwegian
5	Organisation of workshop	Oslo University Hospital	WP14 CENTER-TBI: International workshop on transition of TBI care	26/05/2014	Oslo	Scientific community, Policy Makers, Civil Society	28	International
6	Oral presentation to a wider public	Oslo University Hospital	Country specific organization of TBI care - an overview	26/05/2014	Oslo	Scientific community, Policy Makers, Civil Society	28	International
7	Oral presentation to a wider public	Oslo University Hospital	Emergency and in-hospital TBI care: levels and local practices	26/05/2014	Oslo	Scientific community, Policy Makers, Civil Society	28	International
8	Oral presentation to a wider public	Oslo University Hospital	Discharge policies: home, lower level of care or rehabilitation?	26/05/2014	Oslo	Scientific community, Policy Makers, Civil Society	28	International
9	Oral presentation to a scientific event	University of Oslo	The aims of CENTER-TBI and WP 14	10/06/2014	Oslo	Scientific community	15	Norwegian
10	Poster	Leiden University Medical Center (LUMC) and Medical Center Haaglanden (MCH)	Treatment variation for traumatic acute subdural hematoma - International Neurotrauma Society 2014	20-03-2014 untill 24-03-2014	Budapest	Policy Makers, Scientific Community	1000	International
11	Oral presentation to a scientific event	LUMC and MCH	Factors of influence on surgical decision making for traumatic acute subdural hematoma - International Neurotrauma Society 2014	22/03/2010	Budapest	Policy Makers, Scientific Community	100	International
12	Media briefings	LUMC and MCH	Welke behandeling is het best bij hersenletsel?' - LUMC general website	Oktobre 2013	Leiden	Policy Makers, Scientific Community, medias, civil society	10000	National
13	Presentations	LUMC and MCH	Hersenstichting (Dutch Brain Foundation)	28/03/2014	Utrecht	Policy Makers, Scientific Community	20	National
14	Oral presentation to a scientific event	LUMC and MCH	Wel of niet opereren bij het traumatisch acuut subduraal hematoom?' - Wintermeeting Nederlands	31/01/2014	Utrecht	Scientific Community	50	National

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
			Vereniging voor Neurochirurgie (Dutch Neurosurgical Society)					
15	Oral presentation to a wider public	LUMC and MCH	Invitational Conference choosing Wisely Campaign	10-06-2014 untill 12-06-2014	Rode Hoed & Waag, Amsterdam	Policy Makers, Scientific Community, medias, civil society	100	National
16	Presentations	LUMC and MCH	NetQuRe; Landelijke ketenzorg neurotrauma database van seH-iC- neurochirurgie naar neuro-revalidatie' - Conference Sophia rehabilitatoin center The Hague	18/06/2014	The Hague	Policy Makers, Scientific Community, medias, civil society	500	National
17	Presentations	LUMC and MCH	IBIA 11th world pre-congress organizing meeting The Hague World Forum	27 september 2014	The Hague	Policy Makers, Scientific Community	20	International
18	Poster	LUMC and MCH	Treatment variation for traumatic acute subdural hematoma - Medical Center Haaglanden local conference 2013	29/11/2013	The Hague	Policy Makers, Scientific Community	300	National
19	Poster	LUMC and MCH	Factors of influence on surgical decision making for traumatic acute subdural hematoma - Medical Center Haaglanden local conference 2013	29/11/2013	The Hague	Policy Makers, Scientific Community	300	National
20	Oral presentation to a scientific event	Monash University, University of Antwerp, University of Cambridge	Piloting living systematic reviews in traumatic brain injury - 22nd Cochrane Colloquium	21-26 September 2014	Hyderabad, India	Scientific Community	50	International
21	Oral presentation to a scientific event	Monash University	Piloting living evidence reviews in traumatic brain injury, Trauma 2014	3-5 October 2014	Sydney, Australia	Scientific Community	20	Australia
22	Articles publishes in the popular press	Erasmus University Rotterdam	Adherence to guidelines in traumatic brain injury: a living systematic review [protocol], PROSPERO	24/07/2014	University of York, UK	Scientific Community	Unknown	International
23	Articles publishes in the popular press	University of Antwerp, Monash University	The Glasgow Coma Scale: its reliability, validity, predictive value and responsiveness. A living systematic review, PROSPERO	07/05/2014	University of York, UK	Scientific Community	Unknown	International
24	Articles publishes in the popular press	University of Messina, University of Pecs	Blood-based biomarkers for the diagnosis, characterization and outcome prediction of traumatic brain injuries in adults: a living systematic review, PROSPERO	23/09/2014	University of York, UK	Scientific Community	Unknown	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
25	Articles publishes in the popular press	University of Cambridge	Genetic influences on outcomes from traumatic brain injury: a systematic review and meta-analysis, PROSPERO	06/10/2014	University of York, UK	Scientific Community	Unknown	International
26	Articles publishes in the popular press	University of Cambridge, Monash University	Do cerebral perfusion pressure targets individualised to pressure-reactivity index improve outcomes in moderate to severe TBI? A living systematic review, PROSPERO	11/08/2014	University of York, UK	Scientific Community	Unknown	International
27	Articles publishes in the popular press	Trnava University in Trnava Universitas Tyrnaviensis	"Projekt CENTER-TBI na Katedre verejného zdravotníctva" Project CENTER-TBI at the Department of Public Health	December, 2013	Trnava	Scientific community, Civil society, Policy makers, Medias	1000	Slovakia
28	Oral presentation to a scientific event	University of Stirling	Interpreting health-related quality of life after TBI; QOLIBRI Annual Meeting	14/06/2014	Hamburg	Scientific Community	50	International
29	Oral presentation to a scientific event	University of Stirling	Multidimensional outcome assessment in TBI; 19th Annual EMN Conference	17/10/2014	Ulm	Scientific Community	150	International
30	Organisation of workshop	Oslo University Hospital	Workshop on transitions TBI care	26/05/2014	Oslo, Norway	Scientific Community	30	International
31	Organisation of workshop	Tranava University	Workshop on transitions TBI care	16/10/2014	Trnava, Slovakia	Scientific Community	35	International
32	Organisation of workshop	OBU	Stakeholders views of TBI rehabiliation	28/04/2014	oxford	Scientific Community	8	International
33	Organisation of workshop	OBU	Mapping the TBI rehabiliation journey	21/07/2014	oxford	Scientific Community	10	National
34	Oral presentation to a wider public	OBU	Thames Valley Trauma Network	08/05/2014	oxford	Scientific Community	15	National
35	Oral presentation to a wider public	OBU	Thames Valley Trauma Network	05/09/2014	oxford	Scientific Community	15	National
36	Oral presentation to a scientific event	KI-INCF	Turku Traumatic Brian Injury Symposium	17/01/2014	Turku	Scientific Community	100	International
37	Oral presentation to a scientific event	KI-INCF	Stockholm Brain Institute Annual Retreat	21/02/2014	Stockholm	Scientific Community	50	Sweden
38	Oral presentation to a scientific event	KI-INCF	Open Source Brain Forum meeting	2014-05-13-2014-05-15	Sardinia	Scientific Community	150	International
39	Oral presentation to a scientific event	KI-INCF	Ontario Brain Institute CODE workshop	2014-05-20--2014-05-29	Toronto	Scientific Community	50	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
40	Oral presentation to a scientific event	KI-INCF	Development of Human Brain Image Banks and Age-Specific Normative Brain Atlases	2014-08-28--2014-08-29	Edinburgh	Scientific Community	45	International
41	Oral presentation to a scientific event	KI-INCF	One Mind Summit 2014	2014-05-13--2014-05-17	Washington	Policy makers, Scientific Community, Industry, Civil society	150	International
42	Poster	KI-INCF	Neuroinformatics 2014	2014-08-24--2014-08-27	Leiden	Scientific Community	150	International
43	Oral presentation to a scientific event	UZA	New directions and globalization in TBI research	09/09/2013	Seoul, Korea	Scientific Commity	3000	International
44	Oral presentation to a scientific event	UZA	The potential of compartaive effectivness researhc in TBI	25/10/2013	Hobart, Australia	Scientific community	150	National
45	Organisation of workshop	UZA	CENTER-TBI: An InTBIR project	17-18/10/2013	Vancouver, Canada	Policy Makers	60	International
46	Oral presentation to a scientific event	UZA	Severe TBI: characterizing the target population	15/11/2013	St Louis, USA	Scientific community	200	National
47	Oral presentation to a scientific event	UZA	The potential of comparative effectiveness research in TBI	12/12/2013	Moscow, Russia	Scientific community	300	International
48	Organisation of conference	UZA	New directions and globalization in TBI research	29/01/2014	New York, USA	Scientific community, Policy makers, civil society	100	National
49	Oral presentation to a scientific event	UZA	CENTER-TBI: what it will give for TBI medicine?	17-18/01/2014	Turku, Finland	Scientific community	100	National
50	Oral presentation to a scientific event	UZA	The changing landscape of TBI research	01/03/2014	India	Scientific community	250	National
51	Oral presentation to a scientific event	UZA	New opprotunities for TBI research and collaborations	24-17/04/2014	Wuxi, China	Scientific community	400	National
52	Oral presentation to a scientific event	UZA	CENTER-TBI: a large European study to advance the care for TBI	17/04/2014	USA	Scientific Community	350	International
53	Oral presentation to a scientific event	UZA	TBI: a silent epidemic with hidden consequences	17-18/06/2014	Den Haag, The Netherlands	Scientific Community	150	National
54	Oral presentation to a scientific event	UZA	CENTER-TBI: a large European study to advance the care for TBI	13/06/2014	Salzburg	Scientific Community	150	International
55	Organisation of workshop	UZA	CENTER-TBI	28-19/06/2014	San Francisco, USA	Policy Makers	40	International
56	Organisation of conference	UZA	CENTER-TBI: a large European study to advance the care for TBI	31/07/2014	New York, USA	Scientific community, Policy makers, civil society	80	International

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57	Oral presentation to a scientific event	UZA	CENTER-TBI: a longitudinal comparative effectiveness study	13-17/10/2014	Prague	Scientific commity	1500	International
58	Oral presentation to a scientific event	UZA	Comparative effectivness research to advance the care for TBI	31/10/2014	New Delhi, India	Scientific community	350	National
59	Poster	UZA	Do DTI reproducibility studies agree? A meta-analysis	20/01/2014	Maastricht, NL	Scientific Community	200	International
60	Poster	UZA	Do DTI reproducibility studies agree? A meta-analysis	10-16/05/2014	Milano, Italy	Scientific Community	4000	International
61	Presentations	UZA	CENTER-TBI Neuroimaging	28-29/06/2014	San Francisco, USA	Policy Makers	35	International
62	Press releases	UZA	Val op mijn hoofd heeft mijn karakter veranderd (GAZET VAN ANTWERPEN)	16/10/2013	Belgium	Medias	Unkown	National
63	Press releases	UZA	Meer hersenletsels door alcoholmisbruik thuis (ET BELANG VAN LIMBURG)	16/10/2013	Belgium	Medias	Unkown	National
64	Press releases	UZA	Miljoen mensen kunnen baat hebben" bij breintraumaonderzoek (DE REDACTIE)	12/10/2014	Belgium	Medias	Unkown	National
65	Press releases	UZA	Breintraumaonderzoek UZA kan miljoen mensen helpen (HET LAATSTE NIEUWS)	11/10/2013	Belgium	Medias	Unkown	National
66	Press releases	UZA	UZA coördineert grootschalige Europese studie naar traumatische hersenletsels (ARTSENKRANT nr. 2335)	11/10/2013	Belgium	Medias	Unkown	National
67	Press releases	UZA	Radio Interview with Andrew Maas (RADIO 1)	07/10/2013	Belgium	Medias	Unkown	National
68	Press releases	UP	Mintegy félmilliárd forintot fordítanak a koponyasérülések kutatására (DUNÁNTÚLI NAPLÓ)	18/10/2013	Hungary	Medias	Unkown	National
69	Press releases	UP	A koponyasérülés csöndes járvány (Pécsi STOP)	21/10/2013	Hungary	Medias	Unkown	National
70	Press releases	UP	Mintegy félmilliárd forintot fordítanak a koponyasérülések kutatására (BAMA)	21/10/2013	Hungary	Medias	Unkown	National
71	Press releases	AUT	Researchers seek better brain injury treatments (ADIO NEW ZEALAND NEWS)	15/10/2013	New Zealand	Medias	Unkown	National
72	Press releases	AUT	AUT University is joining European hospitals and institutions to help develop better treatments for traumatic brain injury patients (NZ CITY)	15/10/2013	New Zealand	Medias	Unkown	National
73	Press releases	AUT	AUT UNI Logo blkScientists to tackle traumatic brain injury (SCOOP INDEPENDENT NEWS)	14/10/2013	New Zealand	Medias	Unkown	National

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74	Press releases	University of Cambridge	Cambridge scientists lead brain injury research that could benefit millions (UNIVERSITY OF CAMBRIDGE - RESEARCH NEWS)	11/10/2013	United Kingdom	Medias	Unkown	National
75	Press releases	University of Cambridge	Radio Interview with David Menon	11/10/2013	BBC RADIO	Medias	Unkown	National
76	Articles publishes in the popular press	Faculty of Health Sciences and Social Work Trnava University in Trnava	TRAUMATIC BRAIN INJURY MORTALITY IN THE SLOVAK REPUBLIC IN 2009-2012	14/10/2013	Trnava	Scientific community, Civil society, Policy makers, Medias	100	Slovakia
77	Articles publishes in the popular press	Faculty of Health Sciences and Social Work Trnava University in Trnava	EFFECT OF SEAT-BELT AND CHILD-SEAT INTRODUCTION OF BRAIN TRAUMA RELATED FATALITIES IN CHILDREN AND ADOLESCENTS IN AUSTRIA (1981-2012)	14/10/2013	Trnava	Scientific Community, Civil society, Policy makers, Medias	100	Slovakia
78	Articles publishes in the popular press	Faculty of Health Sciences and Social Work Trnava University in Trnava	THE CHANGING EPIDEMIOLOGY OF TBI: TRAUMATIC BRAIN INJURY DEATHS IN AUSTRIA 1980-2012	14/10/2013	Trnava	Scientific Community, Civil society, Policy makers, Medias	100	Slovakia
79	Articles publishes in the popular press	International Neurotrauma Society	THE AUSTRIAN PROJECT. IMPROVEMENT OF PREHOSPITAL AND EARLY HOSPITAL CARE OF TBI PATIENTS: GOAL AND METHODS OF THE STUDY	01/03/2014	Hungary	Scientific community	1000	International
80	Articles publishes in the popular press	International Neurotrauma Society	THE AUSTRIAN PROJECT IMPROVEMENT OF PREHOSPITAL AND EARLY HOSPITAL CARE OF TBI PATIENTS RESULTS OF THE STUDY	01/03/2014	Hungary	Scientific community	1000	International
81	Articles publishes in the popular press	International Neurotrauma Society	PATTERNS OF SEVERITY AND OUTCOME OF TRAUMATIC BRAIN INJURIES BY LOCATION OF TRAUMA IN AUSTRIA	01/03/2014	Hungary	Scientific community	1000	International
82	Articles publishes in the popular press	International Neurotrauma Society	TRAUMATIC BRAIN INJURY MORTALITY IN THE SLOVAK REPUBLIC IN 2009–2012	01/03/2014	Hungary	Scientific community	1000	International
83	Articles publishes in the popular press	International Neurotrauma Society	TRAUMATIC BRAIN INJURY MORTALITY IN AUSTRIA IN 1980–2012 IN OLDER ADULTS	01/03/2014	Hungary	Scientific community	1000	International

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84	Articles publishes in the popular press	UP	Making inroads in brain health in Hungary – The path to personalized TBI Care	01/08/2014	Brain Trust	Scientific Community	Unknown	International
85	Oral presentation to a scientific event	UZA	MR Imaging of Traumatic Brain Injury: Current Clinical Practice	10-16/05/2014	Milano, Italy	Scientifc Community	6000	International
86	Oral presentation to a scientific event	UZA	Neuroimaging of Movement Disorders	17-22/05/2014	Montreal, Canada	Scientifc Community	2300	International
87	Oral presentation to a scientific event	UZA	Neuroradiological assessment of traumatic brain injury: a pattern-based approach	17-22/05/2014	Montreal, Canada	Scientifc Community	2300	International
88	Oral presentation to a scientific event	UZA	Is there a role for MRI in ligamentous injury of the spine	17-22/05/2014	Montreal, Canada	Scientifc Community	2300	International
89	Oral presentation to a scientific event	UZA	Brain Injury	26-28/06/2014	Wroclaw, Polen	Scientifc Community	85	International
90	Articles publishes in the popular press	UCAM/UZA	Tackling TBI	March 2015	Pan European Networks: Science & Technology 14	Scientifc Community		European
91	Articles publishes in the popular press	UCAM	Head first reshaping how traumatic brain injury is treated	March 2015	Research Horizons			National
92	Poster	ICL	Segmentation of Traumatic Brain Injuries with Convolutional Neural Networks	27-28/08/2015	Turku, Finland	Scientific Community	100	International
93	Oral presentation to a scientific event	ICL	Advanced Machine Learning for MR Image Analysis in TBI	27-28/08/2015	Turku, Finland	Scientific Community	100	International
94	Oral presentation to a scientific event	Erasmus University Rotterdam	Adjusting for confounding by indication in observational studies: An example in traumatic brain injury	25-27/08/2015	Maastricht, NL	Scientific Community		European
95	Oral presentation to a wider public	Oslo University Hospital	Transition of TBI care	05/11/2014	Paris, France	Scientific community, Policy makers	19	International
96	Oral presentation to a scientific event	University of Oslo	(Re)habilitation trajectories, from early to later phases and across social sectors (traumatic brain injuries)	18/11/2014	CHARM, Oslo, Norway	Scientific community	30	International
97	Oral presentation to a wider public	Oslo University Hospital	Center-TBI: Europeisk hodeskadestudie	04/03/2015	Oslo, Norway	Clinicians, Scientific community	62	National
98	Oral presentation to a wider public	Oslo University Hospital	Center-TBI: Europeisk hodeskadestudie	17/04/2015	Sunvollen, Norway	Clinicians, Scientific community	100	National
99	Organisation of workshop	Oslo University Hospital	WP14 CENTER-TBI: International workshop on transition of TBI care	08/05/2015	Oxford, UK	Scientific community, Policy makers	16	International

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100	Oral presentation to a scientific event	Oslo University Hospital	Transition of Care in Traumatic Brain Injury: Deficits in Communication and Information Transfer at Discharge from Acute Hospitalization	19-21.06.2015	ISPRM 2015 Berlin, Germany	Scientific community, Policy makers, civil society	1000	International
101	Oral presentation to a wider public	University of Cambridge	CENTER-TBI	19/06/2015	Sheffield	Scientific community, Civil society, Policy makers, Medias	100	UK
102	Oral presentation to a scientific event	University of Cambridge	CENTER-TBI	21/10/2015	Cambridge	Scientific community, Policy Makers,Civil Society	30	UK
103	Oral presentation to a scientific event	University of Cambridge	CENTER-TBI	21/10/2015	London	Scientifc Community	300	UK
104	Oral presentation to a scientific event	University of Cambridge	Healing, research, teaching: The short way from trainee to ICU-leadership	29-01/10/2014	Barcelona, Spain	Scientific Community	5000	International
105	Oral presentation to a scientific event	University of Cambridge	Organising a large European research project-perils, potential and pitfalls	14/11/2014	Newmarket, UK	Clinicians in anesthesia and intensive care	200	National
106	Oral presentation to a scientific event	University of Cambridge	Joseph Clover Lecture-Mapping unconsciousness: pathological and pharmacological insights	20-21/11/2014	London, UK	Scientific Community	200	National
107	Oral presentation to a scientific event	University of Cambridge	Using advanced imaging to understand pathophysiology and outcome in TBI. Protocols for cerebral perfusion pressure management in TBI. Endophenotpes, partial phenotypes, and endotypes using a new vocabulary to aid precision medicine in TBI.	05-06/11/2015	Bangalore, India	Scientific Community	50	International
108	Oral presentation to a scientific event	University of Cambridge	Translational neuroscience in altered consciousness: clinical perspectives from Cambridge.	07-09-03-2015	Bangalore, India	Scientific Community	50	International
109	Oral presentation to a scientific event	University of Cambridge	Imaging pathophysiology and outcome in TBI.	20/03/2015	Cambridge, UK	Scientific Community	200	National
110	Oral presentation to a scientific event	University of Cambridge	CENTER TBI as a model of collaboration.	27-29/05/2015	Washington, USA	Scientific Community	500	International
111	Oral presentation to a scientific event	University of Cambridge	Using advanced imaging to understand pathophysiology and outcome in TBI.	15-17/06/2015	Prato, Italy	Scientific Community	200	International
112	Oral presentation to a scientific event	University of Cambridge	The initial approach to the comatose patient. Decompressive craniectomy: for which patient?	22-23/06/2015	Brussels, Belgium	Scientific Community	150	International
113	Organisation of conference	University of Cambridge	ICOMETRIX Imaging Meeting	25/06/2015	Cambridge, UK	CENTER TBI collaborators	15	National

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114	Oral presentation to a wider public	University of Cambridge	Disorders of consciousness: Current research landscape	30/06/2015	London, UK		300	National
115	Oral presentation to a scientific event	University of Cambridge	Research progress presentations including a short synthesis on JSMF2 advancement.	04-06/07/2015	Paris, France	Scientific Community	100	International
116	Oral presentation to a scientific event	University of Cambridge	PET imaging as a clinical and research tool in TBI. Acute imaging of severe TBI-what can it give us?	27-28/08/2015	Turku, Finland	Scientific Community	100	International
117	Oral presentation to a scientific event	University of Cambridge	CPD Study Day: The essentials of intensive care. Managing TBI.	02/10/2015	London, UK	Scientific Community	100	National
118	Articles publishes in the popular press	Trnava University	Mortality data: we all rely on it, but how accurate it is?	07/10/2014	Trnava, Slovakia	Scientific community, Civil society, Policy makers, Medias	100	Slovakia
119	Articles publishes in the popular press	Trnava University	Epidemiology and patterns of transport accident relate fatalities in Austria	07/10/2014	Trnava, Slovakia	Scientific community, Civil society, Policy makers, Medias	100	Slovakia
120	Oral presentation to a scientific event	Trnava University	Death certification and mortality reporting across EU countries; 2nd V4 Conference on Public Health 2015: Health for public, public for health	17/09/2015	Zabrze, Poland	Scientific community, Civil society, Policy makers, Medias	150	V4 countries: Poland, Hungary, Czech Republic, Slovakia
121	Articles publishes in the popular press	Trnava University	Death certification and mortality reporting across EU countries	17/09/2015	Zabrze, Poland	Scientific community, Civil society, Policy makers, Medias	unknown	V4 countries: Poland, Hungary, Czech Republic, Slovakia
122	Web sites/Applications	Trnava University	Report on TBI mortality reporting procedures (CENTER-TBI)	From December 2014	Trnava, Slovakia	Scientific community	unknown	Slovakia
123	Web sites/Applications	Trnava University	CENTER-TBI (Collaborative European NeuroTrauma Effectiveness Research in TBI)	From January 2015	Trnava, Slovakia	Scientific community, Civil society, Policy makers, Medias	unknown	Slovakia
124	Web sites/Applications	Trnava University	CENTER-TBI tím naplnil svoj další cieľ, ktorým bolo vyhotovenie systematického prehľadu - Epidemiology of traumatic brain injury in Europe: a living systematic review	From 23.6.2015	Trnava, Slovakia	Scientific community, Civil society, Policy makers, Medias	unknown	Slovakia
125	Web sites/Applications	Trnava University	CENTER-TBI na druhej V4 Konferencii verejného zdravotníctva	From 22.9.2015	Trnava, Slovakia	Scientific community, Civil society, Policy makers, Medias	unknown	Slovakia

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126	Web sites/Applications	Trnava University	CENTER-TBI tím v Antverpách	From 8.10.2015	Trnava, Slovakia	Scientific community, Civil society, Policy makers, Medias	unknown	Slovakia
127	Presentations	Trnava University	Epidemiológia neinfekčných ochorení: Úrazy mozgu, projekt CENTER-TBI	23/02/2015	Trnava, Slovakia	Students	44	Slovakia
128	Organisation of conference	Leiden University Medical Center (LUMC)	Neurotrauma in de regio'	17/06/2015	The Hague	Policy Makers, Scientific Community	200	National
129	Media briefings	Leiden University Medical Center (LUMC)	Welke behandeling is het best bij hersenletsel?' - LUMC general website (https://www.lumc.nl/org/sips/onderzoeken/lopende-onderzoeken/CENTER-TBIenNet-QuRe/)		Leiden	Policy Makers, Scientific Community, medias, civil society	10000	National
130	Presentations	Leiden University Medical Center (LUMC)	IBIA 11th world pre-congress organizing meeting The Hague World Forum		The Hague	Policy Makers, Scientific Community		International
131	Oral presentation to a scientific event	UZA	CENTER-TBI: a longitudinal comparative effectiveness study	13-17/10/2014	Prague, Czech Republic	Scientific community	1500	International
132	Oral presentation to a scientific event	UZA	Neurotrauma clinical research, a new beginning	7.11.2014	Xiamen, China	Scientific community	60	International
133	Oral presentation to a scientific event	UZA	Comparative effectivness research to advance the care for TBI	31.10.2014	New Delhi, India	Scientific community	120	International
134	Oral presentation to a scientific event	UZA	How to design a clinical trial	31.10.2014	New Delhi, India	Scientific community	120	International
135	Oral presentation to a scientific event	UZA	Changing landscape in TBI and its research	19.12.2014	Helsinki, Finland	Scientific community	30	National
136	Oral presentation to a scientific event	UZA	CENTER-TBI: a global initiative	21-24.02.2015	Dubai	Scientific community	1500	International
137	Oral presentation to a scientific event	UZA	The changing landscape of TBI and its treatment	19-21.02.2015	Teheran	Scientific community	150	National
138	Oral presentation to a scientific event	UZA	Brain protection: what's changed in the last 35 years	19.03.2015	Brussels, Belgium	Scientific community	5000	International
139	Oral presentation to a scientific event	UZA	Global collaborations to advance the care for TBI	23-26.04.2015	Kunming city, China	Scientific community	400	National
140	Oral presentation to a scientific event	UZA	Towards global collaborations	27-29/05/2015	Washington, USA	Scientific Community	500	International

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141	Oral presentation to a scientific event	UZA	Towards global collaborations	15-17/06/2015	Prato, Italy	Scientific Community	200	International
142	Oral presentation to a scientific event	UZA	The power of collaboration in TBI research	27-30.08.2015	Zhenzhou, China	Scientific Community	400	National
143	Oral presentation to a scientific event	UZA	Towards global collaborations	25.09.2015	Köln, Germany	Scientific Community	400	International
144	Oral presentation to a scientific event	UZA	Studies, trials and collaboration in TBI	8-12.09.2015	Rome, Italy	Scientific Community	150	International
145	Organisation of workshop	Rigshospitalet	ECoG/EEG workshop	9-10.01.2015	Copenhagen, Denmark	CENTER TBI collaborators	15	International
146	Organisation of workshop	INCF	Analytics Workshop: big data methods for TBI studies	10-12.02.2015	Amsterdam, Netherlands	CENTER TBI collaborators	30	International
147	Articles publishes in the popular press	LUMC	Systematic review and meta-analysis of the treatment of traumatic acute subdural hematoma	31.08.2015	PROSPERO International prospective register of systematic reviews	Scientific Community		International
148	Oral presentation to a scientific event	UZA	Development of a common MRI protocol for the collaborative European neuro trauma effectiveness research in TBI study	March 4-8 2015	Vienna, Austria	Scientifc Community	50	International
149	Poster	UZA	Diffusion tensor imaging of thirty-five anisotropic DTI phantoms for CENTER-TBI	May 30 - June 5 2015	Toronta, Canada	Scientifc Community	Unknown	International
150	Poster	UZA	A highly standardized, easy to produce and cost-effective isotropic PVP diffusion phantom for quality assessment and multi-center studies	May 30 - June 5 2016	Toronta, Canada	Scientifc Community	Unknown	International
151	Poster	UZA	Harmonization of protocols for MRI of the brain in the CENTER-TBI study	August 27-28, 2015	Turku, Finland	Scientifc Community	100	International
152	Oral presentation to a scientific event	UZA	Global collaboration and data sharing in TBI: the example of CENTER-TBI	19.10.2015	Madrid, Spain	Scientific Community	1500	International
153	Oral presentation to a scientific event	UOS	The challenge of multidimensional outcome assessment in TBI	28-31.10.2015	New Delhi, India	Scientific community	120	International
154	Oral presentation to a scientific event	UZA	Recent trials and future goals in neurotrauma	30.10.2015	Vienna, Austria	Scientific Community	50-100	International
155	Oral presentation to a scientific event	UZA	Epidemiology of neurotrauma	04.11.2015	Edinburgh, UK	Scientific Community	50-100	International

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156	Oral presentation to a scientific event	UZA	The challenging landscape of TBI research	05.11.2015	Edinburgh, UK	Scientific Community	50-100	International
157	Organisation of workshop	Trnava University	CENTER-TBI project team meeting: Dissemination of the Significant Results of WP 7	19.11.2015	Trnava, Slovakia	Scientific community	15	Slovak Republic
158	Oral presentation to a scientific event	UZA	Head injury - the bigger picture	8.12.2015	London, UK	Scientific Community	100-150	International
159	Oral presentation to a scientific event	UZA	A global perspective on neurotrauma and the role of neurosurgeons	30.01.2016	Cape-Town, South-Africa	Scientific Community	50-100	International
160	Oral presentation to a scientific event	UZA	Updates on internation initiatives in TBI research	02.02.2016	Cape-Town, South-Africa	Scientific Community	1000	International
161	Oral presentation to a scientific event	UMG	Patient-reported and Performance-based Outcomes in Persons after Mild Traumatic Brain Injury	2-4.02.2016	Cape Town, South Africa	Scientific Community	80	International
162	Oral presentation to a scientific event	UZA	Optimising assessment tools	03.02.2016	Cape-Town, South-Africa	Scientific Community	1000	International
163	Oral presentation to a scientific event	UZA	CENTER-TBI: concept, status and challenges	04.02.2016	Cape-Town, South-Africa	Scientific Community	1000	International
164	Oral presentation to a scientific event	UZA	The changing landscape of TBI care, its research and the role of neurosurgery	03.03.2016	The Hague, NL	Scientific Community	1400	International
165	Organisation of conference	APHP	Invited symposium “A Pathway of Care for Patients with TBI - A European Prospective” during the XIth World Congress on Brain Injury	2-5.03.2016	The Hague, The Netherlands	Scientific Community	over 100	International
166	Organisation of conference	OUS	Invited symposium “A Pathway of Care for Patients with TBI - A European Prospective” during the XIth World Congress on Brain Injury	2-5.03.2016	The Hague, The Netherlands	Scientific Community	over 100	International
167	Organisation of conference	TUCH	Invited symposium “A Pathway of Care for Patients with TBI - A European Prospective” during the XIth World Congress on Brain Injury	2-5.03.2016	The Hague, The Netherlands	Scientific Community	over 100	International
168	Oral presentation to a scientific event	UZA	The changing epidemiology of TBI	17.03.2016	Brussels, Belgium	Scientific Community	6000	International
169	Presentations	Trnava University	Systematický prehľad a jeho využitie pre prax	21.03.2016	Trnava, Slovakia	Students	35	Slovak Republic
170	Articles publishes in the popular press	ICL	Clinician-mimicking program could improve brain injury analysis	12.04.2016	London, UK	Medias	Unknown	National
171	Oral presentation to a scientific event	UZA	Collective European Effectiveness research in TBI	15.04.2016	Barcelona, Spain	Scientific Community	1000	International

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172	Oral presentation to a scientific event	UZA	TBI: past, present and future	21.04.2016	Changsha, China	Scientific Community	50-100	International
173	Oral presentation to a scientific event	UZA	Update on clinical trials and studies in TBI	22.04.2016	Changsha, China	Scientific Community	400	China
174	Articles publishes in the popular press	Trnava University	EPIDEMIOLOGY OF TRAUMATIC BRAIN INJURY IN EUROPE: A LIVING SYSTEMATIC REVIEW	21.-23.4.2016	Vyhne, Slovak Republic	Scientific community	500	Poland, Hungary, Czech Republic, Slovak Republic
175	Articles publishes in the popular press	Trnava University	EURÓPSKY PROJEKT CENTER-TBI NA ZLEPŠENIE DIAGNOSTIKY A LIEČBY ÚRAZOV MOZGU	21.-23.4.2016	Vyhne, Slovak Republic	Scientific community	500	Poland, Hungary, Czech Republic, Slovak Republic
176	Oral presentation to a scientific event	Trnava University	EURÓPSKY PROJEKT CENTER-TBI NA ZLEPŠENIE DIAGNOSTIKY A LIEČBY ÚRAZOV MOZGU; VII. Central European Congress of Disaster and Emergency Medicine	22.04.2016	Vyhne, Slovak Republic	Scientific community, Civil society, Policy makers, Medias	500	Poland, Hungary, Czech Republic, Slovak Republic
177	Poster	Trnava University	EPIDEMIOLOGY OF TRAUMATIC BRAIN INJURY IN EUROPE: A LIVING SYSTEMATIC REVIEW	22.04.2016	Vyhne, Slovak Republic	Scientific community, Civil society, Policy makers, Medias	500	Poland, Hungary, Czech Republic, Slovak Republic
178	Poster	Trnava University	Európsky projekt CENTER- TBI na zlepšenie diagnostiky a liečby úrazov mozgu a jeho poslanie pre verejné zdravotníctvo; XXI. ČERVENKOVE DNI PREVENTÍVNEJ MEDICÍNY	26.04.2016	Tále, Slovak Republic	Scientific community, Civil society, Policy makers, Medias	200	Slovak Republic, Czech Republic
179	Articles publishes in the popular press	Trnava University	Európsky projekt CENTER- TBI na zlepšenie diagnostiky a liečby úrazov mozgu a jeho poslanie pre verejné zdravotníctvo	26.-27.4.2016	Tále, Slovak Republic	Scientific community	200	Slovak Republic, Czech Republic
180	Oral presentation to a scientific event	UZA	The changing landscape of TBI research	27.04.2016	Odessa, Ukrain	Scientific Community	100	International
181	Oral presentation to a scientific event	UZA	Collective European Effectiveness research in TBI	27.04.2016	Odessa, Ukrain	Scientific Community	100	International
182	Web sites/Applications	Trnava University	CENTER-TBI tím aktívne na kongrese vo Vyhniach a konferencii na Táloch	From 6.6.2016 until now	Trnava, Slovakia	Scientific community, Civil society, Policy makers, Medias	unknown	Slovak Republic
183	Oral presentation to a scientific event	UMG	Differences in HRQOL after traumatic brain injury between varying patient groups. Sensitivity of a Disease Specific (QOLIBRI) and a Generic (SF-36) Instrument	9-12.05.2016	Philadelphia, USA	Scientific Community	100	International

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184	Oral presentation to a scientific event	UZA	Update on research in neurotrauma	28.05.2016	Incheon, Korea	Scientific Community	400	International
185	Articles publishes in the popular press	Trnava University	Death certification and mortality reporting across EU countries. In: Health for Public, Public for Health. Heath systems in V4 countries	31.05.2016	Lublin, Poland	Scientific community	unknown	Poland, Hungary, Czech Republic, Slovak Republic
186	Oral presentation to a scientific event	UMG	HRQOLI after TBI in varying patient groups. Sensitivity of a Disease Specific (QOLIBRI) and a Generic (SF-36) Instrument	2-4.07.2016	Eforie Nord, Romania	Scientific Community	200	International
187	Oral presentation to a scientific event	UMG	Outcome evaluation in TBI research. Yearly research seminar Research group “Rehabilitation after trauma”. Focused themes: Outcome evaluation - risk of bias.	27-28.08.2016	Oslo, Norway	Scientific Community	40	Norwegian
188	Oral presentation to a scientific event	UZA	The changing landscape of TBI care and research	30.9.2016	Fukuoka, Japan	Scientific Community	1000	International
189	Press releases	UNIVERSITY OF PECS	Making inroads in brain health in Hungary ? The path to personalized TBI Care	31/08/2014	CENTER-TBI website	Scientific Community		European
190	Articles publishes in the popular press	Trnava University	Systematický prehľad epidemiológie úrazov mozgu v Európe	05/10/2016-07/10/2016	Ostrava, Czech Republic	Scientific Community	unknown	Slovak Republic, Czech Republic
191	Poster	Trnava University	Systematický prehľad epidemiológie úrazov mozgu v Európe; XIII. Ostravské traumatologické dny	06/10/2016	Rožnov pod Radhoštěm, Czech Republic	Scientific Community	100	Slovak Republic, Czech Republic
192	Oral presentation to a scientific event	UZA	Living Systematic Reviews From Evidence to Practice: The InTBIR approach	11/10/2016	Washington, USA	Scientific Community	50-100	International
193	Oral presentation to a scientific event	UZA	New Directions in TBI Research	21/10/2016	Novi Sad, Serbia	Scientific Community	400	International
194	Articles publishes in the popular press	Trnava University	Európsky projekt CENTER-TBI: komplexný prístup k diagnostike a liečbe úrazov mozgu European project CENTER-TBI: comprehensive approach to diagnosis and treatment of brain injuries; In: Lekársky Obzor,65,2016, č. 10, s. 368 - 370, ISSN 0457-4214	30/10/2016	Bratislava, Slovak Republic	Scientific community, Civil society, Policy makers, Medias	unknown	National
195	Articles publishes in the popular press	Trnava University	Death ascertainment and mortality reporting procedure in EU assessed within CENTER-TBI project; In: European Journal of Public Health, Volume 26, Issue suppl_1, 1 November 2016, ckw174.200,	01/11/2016	Vienna, Austria	Scientific Community	unknown	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
196	Oral presentation to a scientific event	UZA	New Paths for the Prevention and Care of TBI	03/11/2016	Pilsen, Czech Republic	Scientific Community	400	International
197	Oral presentation to a scientific event	UZA	Big data analysis in neurotrauma: the CENTER-TBI study	09/11/2016	Bogota, Columbia	Scientific Community	400	International
198	Poster	Trnava University	Death ascertainment and mortality reporting procedure in EU assessed within CENTER-TBI project; 9th European Public Health Conference All for Health, Health for All Vienna	12/11/2016	Vienna, Austria	Scientific Community	unknown	International
199	Oral presentation to a scientific event (2016 Chinese Medical Association traumatic brain injury and cerebral hemorrhage academic conference)	UF	"Blood-Based Traumatic Brain Injury Biomarkers as Diagnostics tests and Drug Development tools"	18/11/2016	Chongqing, China	Scientific Community	500	International
200	Web sites/Applications	Trnava University	Aktívna účasť projektového tímu CENTER-TBI na konferencii v Rožnove a vo Viedni	From 28/11/2016 until now	Trnava, Slovakia	Scientific community, Civil society, Policy makers, Medias	unknown	Slovak Republic
201	Oral presentation to a scientific event	UZA	New Directions in TBI Research	03/12/2016	Taipei, Taiwan	Scientific Community	1000	International
202	Web sites/Applications	Trnava University	Collaborative European NeuroTrauma Effectiveness Research in TBI	From January 2017 until now	Trnava, Slovakia	Scientific community, Civil society, Policy makers, Medias	unknown	Slovak Republic
203	Oral presentation to a scientific event	UZA	Evidence Generation in CENTER-TBI	19/01/2017	Copenhagen, Denmark	Scientific Community	400	International
204	Oral presentation to a scientific event	Trnava University	Projekt CENTER-TBI	09/03/2017	Trnava, Slovakia	Students	30	Slovak Republic
205	Oral presentation to a scientific event	UZA	Chances, opportunities and lessons learned	23/03/2017	Melbourne, Australia	Scientific Community	400	International
206	Poster	OUS	Health professionals' perception on the traumatic brain injury care pathways: A SWOT Analysis.	29/03/2017	New Orleans, USA	Scientific Community, Civil Society, Policy makers	700- 800	International
207	Organization of conference	OUS	Invited symposium "An International Perspective on Long-term Health Care Needs after Traumatic Brain Injury: Challenges and Possible Solutions"	30/03/2017	New Orleans, USA	Scientific Community, Civil society, Policy makers	100-150	International

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208	Oral presentations to a scientific event	OUS	An International Perspective on Long-term Health Care Needs after Traumatic Brain Injury: Challenges and Possible Solutions	30/03/2017	New Orleans, USA	Scientifc Community, Civil Society, Policy Makers	100-150	International
209	Oral presentations to a scientific event	OUS, APHP	An International Perspective on Long-term Health Care Needs after Traumatic Brain Injury: Challenges and Possible Solutions	30/03/2017	New Orleans, USA	Scientifc Community	100-150	International
210	Articles publishes in the popular press	Trnava University	ÚMRTNOSŤ NA ÚRAZY MOZGU VO VYBRANÝCH EURÓPSKYCH KRAJINÁCH – V NEMOCNICI A MIMO NEJ	30/03/2017-01/04/2017	Vyhne, Slovak Republic	Scientific Community	500	Poland, Hungary, Czech Republic, Slovak Republic
211	Oral presentation to a scientific event	Trnava University	ÚMRTNOSŤ NA ÚRAZY MOZGU VO VYBRANÝCH EURÓPSKYCH KRAJINÁCH – V NEMOCNICI A MIMO NEJ; XXI. National Congress of Emergency and Disaster medicine	01/04/2017	Vyhne, Slovak Republic	Scientific Community	500	Poland, Hungary, Czech Republic, Slovak Republic
212	Poster	OUS	Transition of care after Traumatic Brain Injury: Patient experience and satisfaction with discharge from trauma hospital	03-04/05/2017	Trondheim, Norway	Scientific Community, Civil Society	200	National
213	Oral presentation to a scientific event: The 3rd Conference on Critically Ill Children (Chinese Medical Doctor Society)	UF	Biofuild-based Biomarkers for different forms of pediatric brain injuries and insults.	16/04/2017	Beijing, China	Scientific Community	500	International
214	Oral presentation to a scientific event	UZA	Clinical Trials and Personalized Approaches in TBI	20/04/2017	Xi'an, China	Scientific Community	400	International
215	Oral presentation to a scientific event	UZA	All About Registry Data: CENTER-TBI and China-TBI	21/04/2017	Xi'an, China	Scientific Community	400	International
216	Oral presentation to a scientific event	UZA	Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI): A large European study to advance the care for TBI	10/05/2017	Peshawar, Pakistan	Scientific Community	400	International
217	Oral presentation to a scientific event	UZA	Prognosis in TBI – a Basis for Improving Quality of Care	10/05/2017	Peshawar, Pakistan	Scientific Community	400	International
218	Oral presentation to a scientific event	UZA	Progress, Failures and New Approaches for TBI Research – Implications for Neurotrauma	11/05/2017	Salzburg, Austria	Scientific Community	400	International
219	Oral presentation to a scientific event	UZA	New directions for clinical research on TBI: an update on CENTER-TBI	22/05/2017	Brussels, Belgium	Scientific Community	200	International

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220	Oral presentation to a scientific event	UoS	Methods of Collecting Traumatic Brain Injury Outcomes.	04/07/2017	University of Stirling	Scientific Community	60	UK
221	Oral presentation to a scientific event: National Neurotrauma Soc. Symposium 2017	UF	Autoimmunity Response Following TBI: Is It Detrimental or Beneficial?	10/07/2017	Snowbird, Utah, USA	Scientific Community	700	USA
222	Poster	UoS	Patterns of use and quality of reporting of clinical outcome assessments in randomized controlled trials in adult traumatic brain injury	13/07/2017	Imperial College London	Scientific Community	100	International
223	Oral presentation to a scientific event	IRCCS Milan	Contemporary tools of neuro monitoring at the ICU. What is for routine and what is for research?	30/08/2017	Pecs, Hungary	Scientific Community	200	International
224	Oral presentation to a scientific event	UZA	The Burden of TBI: Epidemiology and Health Economics	20/08/2017	Istanbul, Turkey	Scientific Community	500	International
225	Oral presentation to a scientific event: Military Health System Research Symposium 2017	UF	Enhancing the "Regulatory Readiness" of Top TBI Biomarkers Towards FDA Drug Development Biomarker Qualification Program	28/08/2017	Orlando, FL, USA	Scientific Community	100	USA
226	Oral presentation to a scientific event	UZA	The Global Epidemiology of TBI	30/08/2017	Pecs, Hungary	Scientific Community	400	International
227	Oral presentation to a scientific event:7th Pannonian Symposium on CNS injury	UF	Subacute and chronic biomarkers in Traumatic Brain Injury	01/09/2017	Pecs, Hungary	Scientific Community	100	International
228	Oral presentation to a scientific event	UoS	The Glasgow Outcome Scale – Extended: A structured approach to assessing outcome after brain injury.	05/09/2017	Lund, Sweden	Scientific Community	200	International
229	Oral presentation to a scientific event	UoS	The long term consequences of traumatic brain injury.	14/09/2017	Paris, France	Scientific Community	400	International
230	Oral presentation to a scientific event	UZA	CENTER-TBI: Update on Study Status	28/09/2017	Cambridge, UK	Scientific Community	200	International
231	Oral presentation to a scientific event: Singapore Traumatic	UF	Serum biomarkers for mild Traumatic Brain Injury and Concussions: How can they help?	29/09/2017	Singapore. Singapore	Scientific Community	120	Singapore

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	brain Injury Symposium, 2017							
232	Oral presentation to a scientific event: Beijing Tiantan International Forum of Neurosurgery	UF	"Traumatic Brain Injury Spectrum Biomarkers"	04/11/2017	Beijing, China	Scientific Community	500	International
233	Oral presentation to a scientific event	UZA	Optimization of InTBIR datasets for pathoanatomical classification	11/10/2017	Washington, USA	Scientific Community	50-100	International
234	Oral presentation	OUS	Care transition after traumatic brain injury: Discharge process from trauma hospital; patient experience and satisfaction with care transition	13/11/2017	London, UK	Scientific Community, Civil Society, Policy makers,	200	International
235	Poster	icometrix	Automatic Estimation of Midline Shift on acute CT images of Traumatic Brain Injury patients	13-15/11/2017	Lund, Sweden	Clinicians and researchers interested in the exciting field of neurotrauma	50	Nordic
236	Poster	icometrix	Traumatic brain lesion segmentation on CT images with a fully convolutional neural network	28/02/2018-04/03/2018	Vienna	Radiology	50-100	International
237	Oral presentation to a scientific event	UZA	The Lancet Commissioned Issue on TBI	11/10/2018	Washington, USA	Scientific Community	50-100	International
238	Oral presentation	University of Cambridge	Rescuing the Injured Brain	30/01/2015	Basel	Scientific	500	International
239	Oral presentation	University of Cambridge	Chairing, clinical trials meeting	05/03/2015	Cardiff	British Neurosurgery Research Group	100	National
240	Oral presentation	University of Cambridge	Talk on Academic Neurosurgery; RESCUE-ASDH study	22/04/2015	Southampton	Society of British Neurological Surgeons	100	National
241	Oral presentation	University of Cambridge	Clinical trials	09/09/2015	Hull/York	Society of British Neurological Surgeons	100	National
242	Oral presentation	University of Cambridge	"Approaches to Safe Common Clinical Data Sharing-Methodology panel discussion" InTBIR	13/10/2015	Brussels, Belgium	Scientific Community	50-100	International
243	Oral presentation	University of Cambridge	European lecture seminar on Neurotrauma	18/10/2015	Madrid	Scientify community	500	International
244	Meeting	University of Cambridge	British Neurotrauma group meeting - Research in Neurotrauma	23/10/2015	London, Uk	Scientific community	100	National

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245	Oral presentation	University of Cambridge	"Precision medicine approaches in Neuoanesthesia and Neurocritical Care-Traumatic Brain" Annual Scientific Meeting in Anaesthesiology	12/11/2015	Hong Kong, China	Scientific Community	500	International
246	Oral presentation	University of Cambridge	"Big data in medical imaging-paradigm shift or passing fad?" Alan Turing Medical Imaging Workshop	07/12/2015	London, UK	Scientific Community	100	National
247	Oral presentation	University of Cambridge	SARS/RCS meeting Academic Surgery presetnation	06/01/2016	London, UK	Scientific community	100	National
248	Oral presentation	University of Cambridge	"What Do We Know About TBI? Where Do We Need To Go?" Traumatic Brain Injury: Clinical, Pathological and Translational Mechanisms Symposium	25/01/2016	Sante Fe, New Mexico, USA	Scientific Community	250	International
249	Oral presentation	University of Cambridge	"Challenges in severe TBI management" International Neuro Trauma Symposium	01/02/2016	South Africa, Africa	Scientific Community	500	International
250	Oral presentation	University of Cambridge	RESCUE and Clinical trials	02/03/2016	Cambridge, UK	Scientific Community	25	National
251	Oral presentation	University of Cambridge	"Acute brain injury: New aspects" ISICEM	16/03/2016	Brussels, Belgium	Scientific Community	200	International
252	Meeting	University of Cambridge	Chairing, clinical trials sandpit, RESCUE-ASDH, CSDH-Dex investigators meeting	17/03/2016	Cambridge, UK	British Neurosurgery Research Group	25	National
253	Meeting	University of Cambridge	Clincial Trials Chairing	20/04/2016	Newcastle	Society of British Neurological Surgeons	100	National
254	Oral presentation	University of Cambridge	Neurotrauma Clinical Trials, RESCUE-ASDH investigators	30/04/2016	Chicago	Scientific community	500	International
255	Oral presentation	University of Cambridge	"Brain resuscitation and monitoring" and "Stunned, shaken, sheared… saved? Understanding and optimising outcomes from brain injury" Western University/Adult Neurocritical Care Symposium	03/05/2016	London Ontario, Canada	Scientific Community	500	National
256	Oral presentation	University of Cambridge	"Stunned, shaken, sheared… saved? Understanding and optimising outcomes from brain injury" Interdepartmental Division of Critical Care Medicine Visiting Professorship	04/05/2016	London Ontario, Canada	Scientific Community	750	National
257	Oral presentation	University of Cambridge	"TBI-a chronic, progressive, disease with a long therapeutic window" CICM 2016 ASM Minds & Machines Conference	05/06/2016	Adelaide, Australia	Scientific Community	300	National

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258	Oral presentation	University of Cambridge	"Rational approaches to physiological targets in TBI management" St George Hospital and Sutherland Medical Research Foundation	06/06/2016	Sydney, Australia	Scientific Community	350	National
259	Oral presentation	University of Cambridge	Presentation on Neurosurgical Trials	06/06/2016	London	Scientific community	500	International
260	Oral presentation	University of Cambridge	ICP 2016 - invited lecture	28/06/2016	Boston	Scientific community	500	International
261	Oral presentation	University of Cambridge	New Horizons in Brain Trauma, Application of microdialysis to increase our understanding of the pathophysiology of brain injury	30/08/2016	Sydney, Australia	Scientific community	500	International
262	Oral presentation	University of Cambridge	The RESCUEicp results, chairing plenary, talk on advances in Neuro-monitoring, talk on ICP monitoring	04/09/2016	Athens	Scientific community	500	International
263	Meeting and organiser	University of Cambridge	RESCUEicp results, chairing, cranioplasty registry	21/09/2016	Stoke	Society of British Neurological Surgeons	100	National
264	Oral presentation	University of Cambridge	"ICP monitoring" and "MRI for prognostication pros and cons" ESICM	01/10/2016	Milan, Italy	Scientific Community	300	International
265	Oral presentation	University of Cambridge	"GAIN application" InTBIR	11/10/2016	Washington, USA	Scientific Community	100	International
266	Oral presentation	University of Cambridge	key note lecture – The RESCUEicp results	19/10/2016	Rome	Scientific community	500	International
267	Oral presentation	University of Cambridge	The Klaus von Wild lecture. Euroacademia Multidisciplinaria Neurotraumatologica meeting	20/10/2016	Novi Sad	Scientific community	500	International
268	Oral presentation	University of Cambridge	"Current UK sports concussion research landscape-opportunites" 1st Annual UK Sports Concussion Research Symposium	23/11/2016	London, UK	Scientific and sports professionals	150	National
269	Oral presentation	University of Cambridge	Intensive Care Society State of the Art Meeting - RESCUE and clinical trials presentation	05/12/2016	London, UK	Scientific community	250	National
270	Oral presentation	University of Cambridge	New Horizons in Neuotrauma – lecture – The RESCUEicp results	15/12/2016	Chennai, India	Scientific community	500	International
271	Oral presentation	University of Cambridge	The RESCUEicp study - The Critical Care reviews meeting	27/01/2017	Belfast	Scientific Community	100	National
272	Oral presentation	University of Cambridge	SBNS research day - organiser	10/02/2017	London	Society of British Neurological Surgeons	100	National
273	meeting	University of Cambridge	Clinical trials talk/Chairing group	02/03/2017	Birmingham	British Neurosurgery Research Group	100	National

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274	Oral presentation	University of Cambridge	"Traumatic brain injury and large scale collaborative research projects" Rugby Longitudinal Health Studies Meeting	13/03/2017	London, UK	Scientific and sports professionals	Online	National
275	Oral presentation	University of Cambridge	"A patient with severe traumatic brain injury - A patient with severe traumatic brain injury" and "Balancing risks and benefits for second tier therapies - Intracranial hypertension" ISICEM	22/03/2017	Brussels, Belgium	Scientific Community	100	International
276	Oral presentation	University of Cambridge	RESCUE-ADSH Academic Neurosugery	29/03/2017	Oxford	Society of British Neurological Surgeons	100	National
277	Oral presentation	University of Cambridge	Rescuing the injured brain	22/04/2017	Chicago	Scientific community	500	International
278	Oral presentation	University of Cambridge	Rescuing the injured brain (by Skype)	01/05/2017	Skype	Scientific community	500	International
279	Oral presentation	University of Cambridge	"Trials in neurointensive care: failed demonstrations or wrong hypothesis" and "New frontiers in neurointensive care" 28° SMART Symposium	11/05/2017	Milan, Italy	Scientific Community	200	International
280	Oral presentation	University of Cambridge	Rescuing the Injured Brain	14/05/2017	Magdebury	Scientific community	500	International
281	Oral presentation	University of Cambridge	Rescuing the Injured Brain	20/06/2017	Victoria, BC, Canada	Scientific community	500	International
282	Oral presentation	University of Cambridge	“Not all brains are the same” and “TBI; The elderly: decrying nihilism” SMACC	26/06/2017	Berlin, Germany	Scientific Community	1000 and 100 respectively	International
283	Oral presentation	University of Cambridge	"Transformative effects of the InTBIR/CENTER-TBI initiatives for understanding outcome and intervention effects" Frontiers Conference	13/07/2017	London, UK	Scientific Community	250	National
284	Oral presentation	University of Cambridge	Surgical Trials in Neurotrauma	30/08/2017	Hungary	Scientific community	500	International
285	Oral presentation Center-TBI General Assembly	Erasmus MC	Workpackage 11 - Health utility indices and population health	11/09/2017	Antwerp, Belgium	Scientific Community		International
286	Oral presentation	University of Cambridge	"How early imaging following acquired brain injury informs later rehabilitation (PDoC & CENTER-TBI)" BSRM 2017 Annual Scientific Meeting	14/09/2017	Cambridge, UK	Scientific Community	100	National

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287	Oral presentation	University of Cambridge	British Society of Neuro-radiology Cambridge- invited lecture on traumatic brain injury	15/09/2017	Cambridge, UK	Scientific community	100	National
288	Poster - SMDM	Erasmus MC	Health-related quality of life after traumatic brain injury: Deriving a value set for the QOLIBRI-OS and QOLIBRI in 3 European countries	21/09/2017	Leiden, The Netherlands	Scientific Community		International
289	Oral presentation	University of Cambridge	International Decompressive Craniectomy conference, Chair	28/09/2017	Cambridge, UK	Scientific community	500	International
290	Oral presentation	University of Cambridge	key note lecture – New Horizons in Neurotrauma, talk on EANS research fund, meet the experts (decompressive craniectomy)	01/10/2017	Venice, Italy	Scientific community	500	International
291	Oral presentation	University of Cambridge	" Keynote- It takes a global village.."Metabolic Monitoring" Neuorcritical Care Society Annual Meeting	09/10/2017	Hawaii, USA	Scientific Community	300	International
292	Oral presentation	University of Cambridge	Rescuing the Injured Brain	12/10/2017	Royal Society of Medicine, London	Presidential Address	100	National
293	Oral presentation to a scientific event	Trnava University	Deaths due to traumatic brain injury occurring inside hospitals versus outside hospitals in selected European countries.	19/10/2017	Praha, Czech Republic	Scientific Community	unknown	Poland, Hungary, Czech Republic, Slovak Republic
294	Oral presentation to a scientific event: Beijing Tiantan International Forum of Neurosurgery	SJU	Clinical research of TBI in China	04/11/2017	Beijing, China	Scientific Community	500	International
295	Oral presentation to a scientific event	Trnava University	Epidemiologické aspekty úrazov mozgu v SR a Európe; Medziodborové sympózium s medzinárodnou účasťou - CIVILIZAČNÉ OCHORENIA III.	08/11/2017	Trnava, Slovakia	Scientific community, Civil society, Policy makers, Medias	200	Slovak Republic, Czech Republic
296	Invited speaker	Trnava University	Epidemiological aspects of traumatic brain injuries in Europe; The First Nordic Neurotrauma Conference	13/11/2017	Lund, Sweden	Scientific Community	unknown	International
297	Oral presentation	University of Cambridge	Surgical Trials in Neurotrauma	13/11/2017	Lund, Sweden	Scientific community	500	International
298	Oral presentation to a scientific event	UZA	Global Collaborations to Advance the Care for TBI	14/11/2017	Lund, Sweden	Scientific Community	50-100	International
299	Invited Talk	ICL	Unlocking patterns in medical images with AI	18/11/2017	Rotterdam, the Netherlands	Scientific Community	100	International

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300	Oral presentation to a scientific event - international meeting of the Turkish chapter of OHBM, Istanbul	KI-INCF	INCF: Advancing global collaborative brain research	21/11/2017	Istanbul, Turkey	Scientific Community	150	Turkey, Cuba
301	Oral presentation to a scientific event - European Commission workshop on "Conduct disorder and aggression research at EU level – from academic research to biomedical products, treatment recommendations and Public Health uptake"	KI-INCF	INCF: Advancing global collaborative brain research	06/12/2017	European Commission, Brussels, Belgium	Scientific Community	50	European
302	Oral Presentation to a scientific event	UMG	Outcome after TBI	12/12/2017	Seeburg Germany	Scientific Community	20-40	national
303	Interviews national newspaper	LUMC/HMC	Nog altijd een kristallen bol	13/01/2018	Netherlands	General public	>1000	National
304	Oral presentation	LUMC/HMC	Trauma capitis	15/01/2018	Leiden, Netherlands	Students	100	Netherlands
305	Oral presentation	University of Cambridge	Acquired Brain Injury APPG Round Table Discussion on Rehabilitation	30/01/2018	London, UK	Policy makers	50	National
306	Oral presentation to a scientific event	UZA	Precision medicine in TBI: Lessons from the CENTER-TBI European Program	30/01/2018	Singapore	Scientific Community	200	International
307	Oral presentation to a scientific event (WCNR)	UMG	Quality of Life after Traumatic Brain injury (TBI)	02/02/2018	Mumbai, India	Scientific Community	100-200	international
308	Oral presentation to a scientific event	UMG	Anxiety, Depression & Health Related Quality of Life (HRQOL) problems in patients of Traumatic Brain Injury (TBI)	03/02/2018	Pune. India	Scientific Community	100-201	international
309	Oral presentation to a scientific event	UMG	Quality of Life after Traumatic Brain injury (TBI)	03/02/2018	Pune. India	Scientific Community	100-202	international

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
310	Oral presentation to a scientific event (WCNR)	UMG	Quality of Life after Traumatic Brain injury (TBI).	03/02/2018	Pune India	Scientific Community	50-101	international
311	Invited Talk	ICL	Can we build a machine capable of interpreting medical scans with super-human performance?	16/02/2018	Essen, Germany	Scientific Community	200	International
312	Oral presentation	University of Cambridge	"Understanding and improving outcomes from traumatic brain injury" Neurocritical Care Symposium	19/02/2018	Cambridge, UK	Scinetific Community	200	National
313	Oral presentation	LUMC/HMC	Consequences of severe TBI	23/02/2018	Leiden, Netherlands	Students	400	Netherlands
314	Discussant	University of Cambridge	Acute Brain Injury and the Criminal Justice System	27/02/2018	London, UK	Policy makers	50	National
315	Invited Talk	ICL	Deep learning for fully automatic segmentation of normal and pathological structures in medical images	01/03/2018	Vienna, Austria	Scientific Community	500	International
316	Oral presentation	University of Cambridge	"Improving outcomes of TBI" Zimmern Lecture Cambridge Neurological Society Annual Symposium	04/03/2018	Cambridge, UK	Scientific community and public	250	National
317	Oral presentation to a scientific event	UZA	Global collaborations in advancing care for acute traumatic brain injury	09/03/2018	Qatar	Scientific Community	200	International
318	Oral presentation to a scientific event	OUS	Trends and challenges in rehabilitation following traumatic brain injury	14/03/2018	Salamanca, Spain	Scientific Community	700	International
319	Oral presentation to a scientific event	Charité	The negative ultraslow potential, electrophysiological correlate of infarction in the human cortex	15/03/2018	Fukuoka, Japan	Scientific Community	100-200	International
320	Oral presentation to a scientific event	OUS	Trends and challenges in rehabilitation following traumatic brain injury	15/03/2018	Salamanca, Spain	Scientific Community	>100	International
321	Oral presentation	LUMC/HMC	Preventie & behandeling traumatisch hersenletsel	29/03/2018	Arnhem, Netherlands	Scientific Community, Civil Society	200	Netherlands
322	Oral presentation	LUMC/HMC	Evidence based neurosurgery	08/04/2018	Leiden/Delft, Netherlands	Students	100	Netherlands
323	Invited speaker	Trnava University	Epidemiological Studies on Traumatic Brain Injuries in Europe; Data Science, Statistics & Simulation Models – Innovative Technologies for Analysis of Complex Processes and Systems Confrence	11/04/2018	Vienna, Austria	Scientific Community	unknown	International
324	Oral presentation to a scientific event	Trnava University	Epidemiologické charakteristiky úrazov mozgu v Európe; 3. Mezioborové sympozium s mezinárodní účastí	12/04/2018	Rožnov pod Radhoštěm, Czech Republic	Scientific Community	100	Slovak Republic, Czech Republic

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325	Articles publishes in the popular press	UZA	TBI. Can affect anyone, anywhere: Causing death or changing lives forever	12/04/2018	SciTech Europa 2018	Public	unknown	International
326	Oral presentation	LUMC/HMC	Choosing Wisely	18/04/2018	Leiden, Netherlands	Students	100	Netherlands
327	Oral presentation	University of Cambridge	"ICP/CPP monitoring in situ. And now?" UMC ICP Lecture	20/04/2018	Utrecht, Netherlands	Scientific Community	75	National
328	Oral presentation to a scientific event	UZA	The CENTER-TBI Project: Moving towards a living evidence base for TBI	20/04/2018	Shenzhen, China	Scientific Community	200	International
329	Oral presentation to a scientific event - Brain Summit 2019	KI-INCF	CENTER-TBI	24/04/2018	Nobel Forum, Stockholm, Sweden	Scientific Community	200	International (Europe, Canada, USA, Australia, Japan, Malaysia, China)
330	Oral presentation to a scientific event:National head trauma forum	SIU	TBI manageemnt	26/04/2018	Shenzhen, China	Scientific Community	800	natilonal
331	Oral presentation to a scientific event (WCNR)	UMG	Selected Patient-rated outcome after TBI	29/04/2018	Hardassa, Israel	Scientific Community	20-100	international
332	Oral presentation to a scientific event	UZA	International initiatives in clinical research for traumatic brain injury	09/05/2018	Pècs, Hungary	Scientific Community	200	International
333	Oral presentation to a scientific event - Korean Brain Research Institute	KI-INCF	INCF: Advancing global collaborative brain research	10/05/2018	KBRI, Daegu, S Korea	Scientific Community	200	S Korea
334	Oral presentation to a scientific event (WCNR)	UMG	Selected patient-rated outcome after TBI	10/05/2018	Pecs, Hungary	Scientific Community	50-100	international
335	Oral presentation to Government - Korean National Assembly	KI-INCF	INCF: Advancing global collaborative brain research	11/05/2018	Seoul, S. Korea	Government policy makers and press	100	S.Korea
336	Oral presentation to a scientific event	UZA	CENTER-TBI : an innovative and comprehensive approach to evidence generation in tbi	12/05/2018	Nanchang, China	Scientific Community	200	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
337	Oral presentation	LUMC/HMC	Neurotrauma	14/05/2018	Leiden, Netherlands	Students	100	Netherlands
338	Invited speaker	Trnava University	EU registries and dementia development; Old Servants Symposium on Head Trauma in Sports and Risk for Dementia	24/05/2018	Stockholm, Sweden	Scientific Community	unknown	International
339	Oral presentation	LUMC/HMC	How I do it and when I do it	07/06/2018	Leiden, Netherlands	Clinicians, scientific community	75	Netherlands
340	Oral presentation	LUMC/HMC	Ethical aspects and future prospects	08/06/2018	Leiden, Netherlands	Clinicians, scientific community	75	Netherlands
341	Oral presentation to a scientific event	UZA	Traumatic Brain Injury: Re-thinking concepts & new approaches to research	15/06/2018	Montreal, Canada	Scientific Community	50-100	International
342	Invited Talk	ICL	Deep Learning for MR Image Analysis	20/06/2018	Paris, France	Scientific Community	400	International
343	Oral presentation	LUMC/HMC	Challenges to implement evidence based traumatic brain injury guidelines worldwide practice.	21/06/2018	Naples, Italy	Scientific community	300	International
344	Oral presentation to a scientific event	UZA	The living evidence ecosystem: Moving towards living reviews and guidelines	21/06/2018	Naples, Italy	Scientific Community	200	International
345	Oral presentation to a scientific event	UZA	Traumatic Brain Injury: novel approaches to treatment and research	01/07/2018	Road Show, China	Scientific Community	50-100	International
346	Oral presentation	University of Cambridge	"Medicine based evidence and the management of traumatic brain injury" Academic Foundation Programme and NIHR BRC and BTRU Trainees' Annual Research Day	03/07/2018	Cambridge, UK	Scientific Community	75	National
347	Oral presentation to a scientific event - International Brain Initiative coordinating body meeting	KI-INCF	IBI Working Group on Data Sharing: Initial Ideas"	05/07/2018	EPFL, Geneva, Switzerland	Scientific Community, funders, international neuroscience research organisations	15	International (Europe, Canada, USA, Australia, Japan, China)
348	CHE COSA RISCHIAMO CON UN TRAUMA CRANICO (N.Panciera)	UZA	CHE COSA RISCHIAMO CON UN TRAUMA CRANICO (N.Panciera)	24/07/2018	La Stampa	Public	unknown	national
349	Quei colpi di testa che ci fanno molto male e che non sappiamo ancora trattare	UZA	Quei colpi di testa che ci fanno molto male e che non sappiamo ancora trattare	24/07/2018	La Stampa	Public	unknown	national

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
350	Posterpresentation	LUMC/HMC	The Dutch Neurotraumatology Quality Registry'	01/08/2018	Toronto, Canada	Scientific Community	300	International
351	Posterpresentation	LUMC/HMC	Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study	01/08/2018	Toronto, Canada	Scientific Community	300	International
352	Oral presentation	University of Cambridge	"Advanced imaging methods: what is on the horizon?" Neurotrauma 2018 INTS	12/08/2018	Toronto, Canada	Scientific Community	400	International
353	Poster - NeuroTrauma 2018	Erasmus MC	Prevalence of post-concussion-like symptoms in the general population in Italy, The Netherlands and the United Kingdom	13/08/2018	Toronto, Canada	Scientific Community	1000	International
354	Poster - NeuroTrauma 2018	Erasmus MC	Health-related quality of life after traumatic brain injury: Deriving a value set for the QOLIBRI-OS and QOLIBRI in 3 European countries	13/08/2018	Toronto, Canada	Scientific Community	1000	International
355	Oral presentation to a scientific event (WCNR)	UMG	Selected outcome after TBI	13/08/2018	Toronto, Canada	Scientific Community	200-300	international
356	Oral presentation to a scientific event	UZA	New perspectives to clinical tbi research	13/08/2018	Toronto, Canada	Scientific Community	300	International
357	Oral presentation to a scientific event	UZA	Outcome in tbi is multidimensional	14/08/2018	Toronto, Canada	Scientific Community	50-100	International
358	Oral presentation to a scientific event	UZA	CENTER-TBI: el TECg en el mundo real (CENTER-TBI: serious TEC in the real world)	30/08/2018	Rosario, Argentina	Scientific Community	200	International
359	Poster	UP	Introduction of the CENTER-TBI Serum Biobank: current state – future challenges	04/09/2018	Antwerp, Belgium	Scientific Community	100-200	International
360	Oral presentation to a scientific event	University of Sheffield	The CENTER TBI Registry	11/09/2018	Glasgow, UK	Scientific Community	50-100	International
361	Oral presentation to U.K. Medical Research Council	KI-INCF	INCF: Advancing global collaborative brain research	19/09/2018	London, U.K.	Scientific funders	2	U.K.
362	Poster	Trnava University	Deaths and Years of Lost Life Due to Traumatic Brain Injuries in the Paediatric and Adolescent Populations of Europe; In Annals of Epidemiology, Volume 28, Issue 9, Page 663	23/09/2018	OHIO, USA	Scientific Community	unknown	International
363	Poster	Trnava University	Hospital dscharges due to traumatic brain injuries in children and adolescents in 30 European countries; In	23/09/2018	OHIO, USA	Scientific Community	unknown	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
			Annals of Epidemiology, Volume 28, Issue 9, Pages 663–664					
364	Poster	Trnava University	Deaths and Years of Lost Life Due to Traumatic Brain Injuries in the Paediatric and Adolescent Populations of Europe; 2018 Annual Meeting - Applying Epidemiology Across the Lifespan to Improve Health Care, Inform Health Policy and Enhance Population Health	23/09/2018	OHIO, USA	Scientific Community	500	International
365	Poster	Trnava University	Hospital dscharges due to traumatic brain injuries in children and adolescents in 30 European countries; 2018 Annual Meeting - Applying Epidemiology Across the Lifespan to Improve Health Care, Inform Health Policy and Enhance Population Health	23/09/2018	OHIO, USA	Scientific Community	500	International
366	Oral presentation to a scientific event	Charité	Workshop: Clinical Monitoring of Spreading Depolarizations	25/09/2018	Boca Raton, USA	Scientific Community	35	International
367	Oral presentation to a scientific event	Charité	Spreading Depolarizations: The Silent Culprit of Secondary Injury that You've Been Missing	27/09/2018	Boca Raton, USA	Scientific Community	200-300	International
368	Oral presentation	University of Cambridge	"Rational TBI management in the context of negative trails: understanding pathphysiological heterogeneity and using neuromonitoring for pragmatic precision medicine" and "Prognostication in traumatic brain injury Traumatic brain injury: A chronic progressive disease with a long therapeutic window" VIVU/ST-väst Postgraduate Program	27/09/2018	Gothenburg, Sweden	Scientific Community	50	National
369	Oral presentation educational	LUMC/HMC	Severe traumatic brain injury	02/10/2018	The Hague, Netherlands	Clincians and nurses	50-100	National
370	Oral presentation to a scientific event	UZA	TBI research: opportunities and challenges	04/10/2018	Galveston, USA	Scientific Community	200	International
371	Oral presentation to a scientific event	UZA	Critical Appraisal of the BTF Guidelines	20/10/2018	Brussels, Belgium	Scientific Community	50	International
372	Oral presentation to a scientific event	UZA	The CENTER-TBI project and recommendations to improve care and research	21/10/2018	brussels, Belgium	Scientific Community	200	International
373	Oral presentation to a scientific event	University of Cambridge	New Horizons in the management of TBI	15/01/2018	Leuven, Belgium	Scientific Community	20	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
374	Oral presentation to a scientific event	University of Cambridge	Euroacademia- lessions learnt from trials	08/05/2018	Pecs, Hungary	Scientific Community	100	International
375	Oral presentation to a scientific event	University of Heidelberg	Is there a breakthrough on the horizon in TBI care?	08/05/2018	Pecs, Hungary	Scientific Community	100	International
376	Oral presentation to a scientific event	University of Cambridge	Clinical Trials in TBI	20/06/2018	Naples, Italy	Scientific Community	300	International
377	Oral presentation to a scientific event	ICL	Deep Learning in Medical Imaging: Beyond Human-level Performance	21/09/2018	London, UK	Scientific Community, Industry, Policy Makers	300	International
378	Oral presentation to a scientific event	University of Heidelberg	Breakthroughs in the treatment of TBI – Past and Present	12/10/2018	Seoul, South Korea	Scientific Community	200-300	International
379	Oral presentation to a scientific event	ICL	AI in Medical Imaging	30/10/2018	London, UK	Policy Makers	200	International
380	Oral presentation to a scientific event	ICL	Machine Learning in Medical Imaging	02/11/2018	London, UK	Clinicians, scientific community	200	National
381	Oral presentation to a scientific event	ICL	Machine Intelligence in Clinical Imaging	06/11/2018	London, UK	Scientific Community, Policy makers	100	National
382	Poster	KI-INCF	The CENTER-TBI project and the Neuroinformatics platform	21/11/2018	Brussels, Belgium	Scientific community and public	50-100	International
383	Oral presentation to a scientific event	UMG	Selected outcome after TBI	29/11/2018	Jerusalem, Israel	Scientific Commuinity	40	International
384	Oral presentation to a scientific event	KI-INCF	Redefining Neurodegeneration: A global collaboration to share deep phenotyping data	04/12/2018	Toronto, Canada	Scientifc Community	50-100	International
385	Oral presentation,panel discussion and press conference	KI-INCF	Data Collection, Platforms & Sharing - European (/Global) Perspective.	06/12/2018	Toronto, Canada	Scientifc Community	50-100	International
386	Oral presentation to a scientific event	University of Cambridge	EANS Neurotrauma- overview of RCTs	14/12/2018	Lund, Sweden	Scientific Community	100	International
387	Oral presentation to a scientific event	University of Heidelberg	Registerstudien und „high resolution monitoring“: Big Data - gib es einen Nutzen für den Alltag?	17/01/2019	Berlin, Germany	Scientific Community	100-200	National
388	Oral presentation to a scientific event	University of Cambridge	Connecting injury, pathophysiology, and outcome: A manifesto for rational critical care in TBI	06/03/2019	Pittsburgh, USA	Scientific and clinical researchers and clinicians	500	International
389	Oral presentation to a scientific event	UMG	Assessing Outcome after TBI across Europe – Further Experiences from Center-TBI	13/03/2019	Toronto Canada	Scientific Commuinity	200	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
390	Poster	Oslo University Hospital	Development of a Minimum Reporting Set for Rehabilitation Interventions Based on ICSO-R	14/03/2019	Toronto, Canada	Scientific Community	800	International
391	Oral presentation to a scientific event	Oslo University Hospital	Pediatric Traumatic Brain Injury in South-Eastern Norway- 6 months outcome	16/03/2019	Toronto, Canada	Scientific Community	100	International
392	Oral presentation	KI-INCF	INCF, a standards organization for Neuroscience	19/03/2019	Shanghai	Scientifc Community	50	International
393	Oral presentation to a scientific event	ICL	Hopes and Hurdles for AI in Radiology	20/03/2019	Cambridge, UK	Clinicians, scientific community	100	National
394	Oral presentation	KI-INCF	Advancing global collaborative research	04/04/2019	Brussels, Belgium	Scientific community, Civil society, Policy makers	48	International
395	Oral presentation to a scientific event	UMG	Patient-Reported and Performance based Outcome after TBI – European Experiences from Center-TBI	10/04/2019	Cluj-Napoca, Romania	Scientific Commuinity	50	International
396	Oral presentation to a scientific event	Oslo University Hospital	Transition of care following traumatic brain injury	22/04/2019	Richmond, USA	Scientific Community	25	International
397	Oral presentation to a scientific event	Oslo University Hospital	How can we evaluate and improve services to TBI patients	22/04/2019	Richmond, USA	Scientific Community	25	International
398	Oral presentation to a scientific event	University of Heidelberg	Long pressure reactivity index (LPRx) predicts outcome in 205 patients with TBI	08/05/2019	Würzburg, Germany	Scientific Community	50-100	National
399	Oral presentation to a scientific event	University of Heidelberg	Traumatic brain injury – provision of care, registries, trials and more	08/05/2019	Würzburg, Germany	Scientific Community	500	International
400	Oral presentation to a scientific event	University of Cambridge	Traumatic brain injury in an elderly population	11/05/2019	Dublin, Ireland	Clinicians	250	International
401	Oral presentation to a scientific event	University of Heidelberg	Traumatic Brain Injury (TBI) – Current trends in diagnosis and treatment	21/05/2019	Stockholm, Sweden	Scientific Community	300	International
402	Oral presentation to a scientific event	Charité	SAH: The importance of cortical spreading depression	24/05/2019	Milano, Italy	Scientific Community	200	International
403	Oral presentation to a scientific event	Charité	20 years of research on cortical spreading depolarizations: answered and unanswered questions	26/06/2019	Amsterdam, Netherlands	Scientific Community	200	International
404	Oral presentation to a scientific event	UMG	Selected Outcome after TBI	28/06/2019	Pittsburgh, USA	Scientific Commuinity	150	International
405	Oral presentation to a scientific event	Charité	Monitoring of spreading depolarizations on the ICU	01/07/2019	Yokohama, Japan	Scientific Community	100	International
406	Oral presentation to a scientific event	Charité	Correlates of spreading depolarization, spreading depression and negative ultraslow potential in human epidural versus subdural electrocorticography	03/07/2019	Yokohama, Japan	Scientific Community	100	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
407	Oral presentation to a scientific event	Charité	Moderator of the open discussion (clinical issues: SD, seizures and epilepsy)	03/07/2019	Yokohama, Japan	Scientific Community	100	International
408	Oral presentation to a scientific event	Charité	Correlates of spreading depolarization, spreading depression and negative ultraslow potential in human epidural versus subdural electrocorticography	05/07/2019	Yokohama, Japan	Scientific Community	200	International
409	Oral presentation to a scientific event	Charité	The continuum of spreading depolarizations in acute cortical lesion development: Examining Leão's legacy	07/07/2019	Yokohama, Japan	Scientific Community	200	International
410	Oral presentation	University of Cambridge (MRC)	Realistic & Robust Reproducible Research	11/07/2019	Data Champions Forum	Scientific community	20	National
411	Oral presentation to a scientific event	University of Cambridge	The RESCUE-ASDH trial	20/08/2019	Colton, CA, USA	Students + Scientific Community	20	International
412	Oral presentation to a scientific event	LUMC/HMC	Role of ICP Monitoring in TBI Care- Evidence based consensus and CENTER-TBI first results	24/08/2019	Neurotrauma conference Agra 2019	Policy Makers, Scientific Community	500	International
413	Oral presentation to a scientific event	UMG	Center-TBI Experiences and Results	06/09/2019	Beijing China	Scientific Commuinity	80	International
414	Oral presentation to a scientific event	University of Cambridge	Developing Precision Medicine Approaches for TBI	09/09/2019	Leuven, Belgium	Scientific community	500	International
415	Poster	University of Heidelberg	Outcome prediction of the pressure reactivity index (PRx) and long pressure reactivity index (LPRx) in TBI patients: a CENTER-TBI study	11/09/2019	Leuven, Belgium	Scientific Community	20-30	International
416	Oral presentation to a scientific event	ICL	Spot-the-Lesion: Image- based disease detection with deep learning	19/09/2019	London, UK	Clinicians, scientific community	100	National
417	Oral presentation to a scientific event	UP	Biomarkers and their role in TBI	24/09/2019	Dublin, Ireland	Scientific Community	200-300	International
418	Poster	LUMC/HMC	Randomized Evaluation of Surgery in Elderly with a Traumatic Acute Subdural Hematoma (RESET-ASDH): protocol of a pragmatic randomized controlled trial	24/09/2019	Dublin (EANS 2019)	Policy Makers, Scientific Community	300	International
419	Oral presentation to a scientific event	LUMC/HMC	Functional outcome after surgical or conservative treatment of acute subdural hematoma: a living systematic review	29/09/2019	Dublin (EANS 2019)	Policy Makers, Scientific Community	40	International
420	Oral presentation to a scientific event	LUMC/HMC	CENTER-TBI first results	29/09/2019	Dublin (EANS 2019)	Policy Makers, Scientific Community	500	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
421	Oral presentation	University of Cambridge (MRC)	Practical tools to make data research easier and better	30/09/2019	ESICM LIVES 2019, Berlin	Scientific Community	30	International
422	Oral presentation to a scientific event	UP	Development of a Serum Biobank and Preliminary Biomarker Investigations in a Large Scale International TBI Study	03/10/2019	Milazzo, Italy	Scientific Community	50-100	International
423+434	Poster	UZA/UP	Biobanks and traumatic Brain Injury: Experience from CENTER-TBI	08/10/2019	Lübeck, Germany	Scientific Community	100-200	International
425	Oral presentation to a scientific event	Oslo University Hospital	Transition of care following traumatic brain injury: preliminary results from the Center TBI study	09/10/2019	Oslo, Norway	Scientific Community	110	International
426	Oral presentation educational	LUMC/HMC	Severe traumatic brain injury	10/10/2019	The Hague, Netherlands	Clincians and nurses	50-100	National
427	Oral presentation to a scientific event	University of Cambridge	InTBIR the next phase	30/10/2019	Bethesda, USA	Scientific Community + Funders	100	international
428	Oral presentation to a scientific event	University of Cambridge	GAIN and preliminary results from CENTER-TBI	30/10/2019	Bethesda, USA	Scientific Community	50	International
429	Poster	Erasmus MC	Prevalence rates of post-concussion symptoms in complicated vs uncomplicated mild traumatic brain injury patients at three and six months post-injury: Results from the CENTER-TBI study.	18/11/2019	Lund, Sweden	Scientific Community	200	International
430	Oral presentation to a scientific event	University of Cambridge	HDF5-Based Data Format for Archiving Complex Neuro-monitoring Data in Traumatic Brain Injury Patients	01/06/2016	Boston, USA	Scientific Community, Clinicians		
431	Oral presentation to a scientific event	University of Cambridge	New Horizons in the management of TBI	15/01/2018	Leuven, Belgium	Scientific Community	20	International
432	Oral presentation to a scientific event	University of Cambridge	Euroacademia- lessions learnt from trials	08/05/2018	Pecs, Hungary	Scientific Community	100	International
433	Oral presentation to a scientific event	University of Cambridge	Clinical Trials in TBI	20/06/2018	Naples, Italy	Scientific Community	300	International
434	Oral presentation to a scientific event	ICL	Deep Learning in Medical Imaging: Beyond Human-level Performance	21/09/2018	London, UK	Scientific Community, Industry, Policy Makers	300	International
435	Oral presentation to a scientific event	ICL	AI in Medical Imaging	30/10/2018	London, UK	Policy Makers	200	International
436	Oral presentation to a scientific event	ICL	Machine Learning in Medical Imaging	02/11/2018	London, UK	Clinicians, scientific community	200	National

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
437	Oral presentation to a scientific event	ICL	Machine Intelligence in Clinical Imaging	06/11/2018	London, UK	Scientific Community, Policy makers	100	National
438	Oral presentation to a scientific event	University of Cambridge	EANS Neurotrauma- overview of RCTs	14/12/2018	Lund, Sweden	Scientific Community	100	International
439	Oral presentation to a scientific event	University of Cambridge	Distinguished Investigator Lecture: Critical Care of Traumatic Brain Injury: An exercise in clinical kintsugi	16/02/2019	Orlando, Florida	Scientific Community, Clinicians	200	International
440	Oral presentation to a scientific event	University of Cambridge	Connecting injury, pathophysiology, and outcome: A manifesto for rational critical care in TBI	06/03/2019	Pittsburgh, USA	Scientific and clinical researchers and clinicians	500	International
441	Oral presentation to a scientific event	ICL	Hopes and Hurdles for AI in Radiology	20/03/2019	Cambridge, UK	Clinicians, scientific community	100	National
442	Oral presentation to a scientific event	University of Cambridge	Traumatic brain injury in an elderly population	11/05/2019	Dublin, Ireland	Clinicians	250	International
443	Oral presentation to a scientific event	University Hospital Heidelberg	Long pressure reactivity index (LPRx) predicts outcome in 205 patients with TBI	12/05/2019	Würzburg, Germany (Annual meeting of the German Society of Neurosurgery 2019)	Scientific Community	unknown	National
444	Oral presentation to a scientific event	University of Cambridge	Neuroimaging, CSF and plasma biomarkers in TBI	01/07/2019	Oslo, Norway	Scientific Community, Clinicians	200	International
445	Oral presentation	University of Cambridge (MRC)	Realistic & Robust Reproducible Research	11/07/2019	Data Champions Forum	Scientific community	20	National
446	Oral presentation to a scientific event	University of Cambridge	The RESCUE-ASDH trial	20/08/2019	Colton, CA, USA	Students + Scientific Community	20	International
447	Oral presentation to a scientific event	University of Cambridge	Automatic Pulse Classification for Artefact Removal Using SAX Strings, a CENTER-TBI Study	07/09/2019	Leuven, Belgium	Scientific Community, Clinicians	unknown	International
448	Oral presentation to a scientific event	University of Cambridge	Patient's Clinical Presentation and CPPopt Availability: Any Association?	07/09/2019	Leuven, Belgium	Scientific Community, Clinicians	unknown	International
449	Oral presentation to a scientific event	University of Cambridge	Python-Embedded Plugin Implementation in ICM+: Novel Tools for Neuromonitoring Time Series Analysis with Examples Using CENTER-TBI Datasets	07/09/2019	Leuven, Belgium	Scientific Community, Clinicians	unknown	International
450	Oral presentation to a scientific event	University of Cambridge	Self-Supervised Artefact Rejection for Intensive Care Waveform Data Using Deep Generative Learning	07/09/2019	Leuven, Belgium	Scientific Community, Clinicians	unknown	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
451	Oral presentation to a scientific event	University of Cambridge	Analysis of Cardio-Cerebral Crosstalk Events in an Adult Cohort from the CENTER-TBI Study	07/09/2019	Leuven, Belgium	Scientific Community, Clinicians	unknown	International
452	Poster	University Hospital Heidelberg	Outcome prediction of the pressure reactivity index (PRx) and long pressure reactivity index (LPRx) in TBI patients: a CENTER-TBI study	08/09/2019	Leuven, Belgium (ICP 2019 Conference)	Scientific Community	unknown	International
453	Oral presentation to a scientific event	University of Cambridge	Developing Precision Medicine Approaches for TBI	09/09/2019	Leuven, Belgium	Scientific community	500	International
454	Oral presentation to a scientific event	University of Cambridge	Stratification for mild TBI: what are our important markers?,	10/09/2019	Leuven, Belgium	Scientific Community, Clinicians	500	International
455	Oral presentation to a scientific event	ICL	Spot-the-Lesion: Image- based disease detection with deep learning	19/09/2019	London, UK	Clinicians, scientific community	100	National
456	oral presesentation to a scientific event	University of Milano - Bicocca	Characteristics and outcomes of elderly traumatic brain injured patients admitted to ICU. Data from Center-TBI	28/09/2019	ESICM LIVES 2019, Berlin	Scientifc Community	unknown	International
457	oral presesentation to a scientific event	University of Milano - Bicocca	Acute kidney injury in traumatic brain injured patients: results from the CENTER TBI study	28/09/2019	ESICM LIVES 2019, Berlin	Scientifc Community	unknown	International
458	Poster	University of Milano - Bicocca	Incidence, risk factors, and effects on outcome of ventilator associated pneumonia in patients with traumatic brain injury: data from the CENTER TBI study	28/09/2019	ESICM LIVES 2019, Berlin	Scientifc Community	unknown	International
459	Poster	University of Milano - Bicocca	Prevalence and timing of tracheostomy in traumatic brain injured patients: a secondary analysis from the CENTER-TBI study	28/09/2019	ESICM LIVES 2019, Berlin	Scientifc Community	unknown	International
460	Poster	University of Milano - Bicocca	Hyperoxia in Traumatic Brain Injury. Data from Center-TBI	28/09/2019	ESICM LIVES 2019, Berlin	Scientifc Community	unknown	International
461	Oral presentation	University of Cambridge (MRC)	Practical tools to make data research easier and better	30/09/2019	ESICM LIVES 2019, Berlin	Scientific Community	30	International
462	Oral presentation to a scientific event	University Hospital Antwerp	Inequalities of care: are they a destiny	04/10/2019	Pannonians, Messina, Sicily	Scientific Community	unknown	International
463	Oral presentation to a scientific event	University Hospital Antwerp	CENTER-TBI and international collaborations	04/10/2019	Pannonians, Messina, Sicily	Scientific Community	unknown	International
464	Oral presentation to a scientific event	University of Cambridge	Individualizing Cerebral Perfusion Pressure Using The Lower Limit of Reactivity: A CENTER-TBI High-Resolution Sub-Study Analysis	14/10/2019	Vancouver, Canada	Scientific Community, Clinicians	150	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
465	Lecture	University of Milano - Bicocca	Come sta cambiando il trattamento del traumatic brain injury	15/10/2019	73° CONGRESSO NAZIONALE SIAARTI – ICARE - INTENSIVE CARE ANAESTHESIA RESUSCITATION EMERGENCY & PAIN	Scientifc Community		International
466	Oral presentation to a scientific event	University of Cambridge	Kintsugi and the art (and science) of TBI care	17/10/2019	Ann Arbor, USA	Scientific Community, Clinicians, Academics	200	International
467	Poster	UMG	ISOQOL: Patient-Reported and Performance based Outcomes after TBI – European Experiences from Center-TBI.	20/10/2019	San Diego, USA	Scientific Community	300	international
468	Oral presentation to a scientific event	University of Cambridge	CENTER-TBI data: preliminary GWAS results	23/10/2019	Bethesda, USA	Scientific Community, Clinicians	100	International
469	Oral presentation to a scientific event	University of Cambridge	Imaging and blood biomarkers in TBI	24/10/2019	Bethesda, USA	Scientific Community + Funders	100	International
470	Oral presentation to a scientific event	University of Cambridge	GAIN Consortium: Progress and preliminary results	24/10/2019	Bethesda, USA	Scientific Community, Clinicians	100	International
471	Oral presentation to a scientific event	University of Cambridge	InTBIR the next phase	30/10/2019	Bethesda, USA	Scientific Community + Funders	100	international
472	Oral presentation to a scientific event	University of Cambridge	GAIN and preliminary results from CENTER-TBI	30/10/2019	Bethesda, USA	Scientific Community	50	International
473	Oral presentation to a scientific event	University of Cambridge	Advanced Imaging in Severe TBI, World Congress of Neurology, Dubai	30/10/2019	Dubai	Scientific Community, Clinicians	200	International
474	Invited speaker	Oslo University Hospital	Center-TBI: Challenges and opportunities	31/10/2019	Copenhagen, Denmark	Scientific Community	50	International
475	Oral presentation to a scientific event	University Hospital Antwerp	The epidemiology of TBI and the role of Neurosurgery	6-7/11/2019	Global Neuro Course, Edinburgh, UK	Scientific Community	unknown	International
476	Oral presentation to a scientific event	University Hospital Antwerp	The contemporary landscape of TBI	6-7/11/2019	Global Neuro Course, Edinburgh, UK	Scientific Community	unknown	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
477	Oral presentation to a scientific event	University Hospital Heidelberg	Outcome prediction with the long pressure reactivity index (LPRx) and its derived optimal cerebral perfusion pressures in 224 adult TBI patients	08/11/2019	Mainz, Germany	Scientific Community	unknown	National
478	Lecture	University of Milano - Bicocca	Extracranial Complications of TBI	10/11/2019	Critical Care CANADIAN FORUM	Scientifc Community		International
479	Oral presentation to a scientific event	University of Cambridge	Outcome and impact of traumatic brain injury: National and international insights	11/11/2019	London, UK	Scientific Community, Clinicians	100	National
480	Oral presentation to a scientific event	University Hospital Heidelberg	Injury mechanisms and severity in pediatric traumatic brain injury patients admitted to the ward or intensive care unit: A Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study	18/11/2019	Lund, Sweden (NNC 2019)	Scientific Community	unknown	International
481	Oral presentation to a scientific event	University Hospital Antwerp	CENTER-TBI: the power of numbers and multidisciplinary collaboration	18/11/2019	NNC 2019, Lund, Sweden	Scientific Community	unknown	International
482	Oral presentation to a scientific event	University Hospital Antwerp	Traumatic brain injury in the ER: CT for all?	18/11/2019	NNC 2019, Lund, Sweden	Scientific Community	unknown	International
483	Oral presentation to a scientific event	University of Stirling	Quality of life after traumatic brain injury	19/11/2019	Lund, Sweden	Scientific Community	200	International
484	Invited speaker	Oslo University Hospital	Rehabilitation pathways after TBI	20/11/2019	Lund; Sweden	Scientific Community	200	International
485	Oral presentation to a scientific event	University of Cambridge	Traumatic Brain Injury (TBI): Diagnosis and treatments - from past to future.	27/11/2019	Stockholm	Scientific Community, Clinicians, Academics	200	International
486	Oral presentation	University of Cambridge	Imaging pathophysiological derangements following TBI: Implications for Clinical Management	06/12/2019	London, UK	Scientific Community, Clinicians	200	National
487	Oral presentation to a scientific event	University of Cambridge	Neurotrauma update	17/12/2019	Cambridge, UK	Scientific Community, Clinicians, Academics	200	National
488	Webinar	University of Cambridge	Rescuing the injured brain	06/01/2020	Online	Scientific Community, Clinicians	Unkown (online)	International
489	Oral presentation to a scientific event	ICL	Good and bad data in machine learning for imaging	23/01/2020	London, UK	Scientific Community	200	National
490	Lecture	University of Milano - Bicocca	Traumatic brain injury 2020: changing scenario	26/01/2020	International Winter Symposium in	Scientifc Community		International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
					Intensive Care Medicine 2020			
491	Lecture	University of Milano - Bicocca	Extracranial complications in TBI	26/01/2020	International Winter Symposium in Intensive Care Medicine 2020	Scientifc Community		International
492	Oral presentation to a scientific event	UMG	CENTER-TBI: Multi-dimensional outcome assessment. Center-TBI/WP 10.	29/01/2020	Rotterdam, the Netherlands	CenterTBI collaborators	200	international
493	Oral presentation to a scientific event	University Hospital Heidelberg	Injury Mechanisms and Severity In Pediatric Traumatic Brain Injury Patients Admitted To The Ward Or Intensive Care Unit – The European Perspective	25/04/2020	Online (Annual meeting of the AANS 2020)	Scientific Community	unknown	International
494	Oral presentation to a scientific event	UMG	6th EAN Paris (Lecture): Sequelae of Mild Tbi: Center-Tbi Experiences and Results.	23/05/2020	Paris, France	Scientific Community	800	international
495	Oral presentation to a scientific event	University Hospital Heidelberg	Post-concussive symptoms in children and adolescents with traumatic brain injury: a CENTER-TBI study	26/05/2020	Online (EAN Virtual Congress 2020)	Scientific Community	unknown	International
496	Oral presentation to a scientific event	University of Cambridge	Update from CENTER-TBI: Insights and intuitions	16/06/2020	Online	Scientific Community, Clinicians	Unknown (online)	International
497	Oral presentation to a scientific event	University Hospital Heidelberg	Prediction of post-concussive symptoms in children and adolescents with traumatic brain injury: A CENTER-TBI study analysis	21/06/2020	Online (Annual meeting of the German Society of Neurosurgery 2020)	Scientific Community	unknown	National
498	Inaugural Lecture	University of Cambridge	Visiting Professor for contributions to the field of Neurosurgeryand Neurotraumatology	29/06/2020	Milan, Italy	Scientific Community, Clinicians, Academics	Unkown	International
499	Oral presentation to a scientific event	ICL	Training data for deep learning: what is needed?	15/07/2020	Virtual ECR 2020	Scientific Community	500	International
500	Lecture	University of Milano - Bicocca	ESSENTIAL MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY: PRACTICAL ADVICE FROM EXPERT CONSENSUS	02/09/2020	Global Neuro Webinar	Scientifc Community		International
501	Webinar	University of Cambridge	Delivering neurotrauma research in low and middle income countries	22/09/2020	Online	Scientific Community, Clinicians	Unkown (online)	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
502	Oral presentation to a scientific event	University of Cambridge	Imaging and Biomarkers in TBI: results from CENTER-TBI, Royal College of Emergency Medicine Annual Conference	01/10/2020	London, UK	Scientific Community, Clinicians	Unkown (online)	National
503	Oral presentation to a scientific event	University of Cambridge	The relationship between serum biomarkers of traumatic brain injury (TBI) and Magnetic Resonance Imaging (MRI) in patients discharged from the emergency department (ED) with a normal acute CT	01/10/2020	London, UK	Scientific Community, Clinicians	Unkown (online)	National
504	Oral presentation to a scientific event	University of Cambridge	The relationship between intracranial MRI abnormalities and post-concussive symptoms in ED patients with a normal CT: as demonstrated on the Rivermead Post Concussion Symptom Questionnaire (RPQ)	01/10/2020	London, UK	Scientific Community, Clinicians	Unkown (online)	National
505	Oral presentation to a scientific event	University of Cambridge	Acute magnetic resonance imaging for mild traumatic brain injury	01/10/2020	London, UK	Scientific Community, Clinicians	Unkown (online)	National
506	Oral presentation to a scientific event	ICL	The Quest for Robust Machine Learning	08/10/2020	Virtual MICCAI Conference	Scientific Community	200	International
507	Oral presentation to a scientific event	University of Sheffield	TBI Update	14/10/2020	RCEM VSC On line, Mancheser	Scientific Community	unknown	International
508	Oral presentation to a scientific event	University of Cambridge	Imaging in brain injury	01/11/2020	Shanghai, China	Scientific Community, Clinicians	Unkown (online)	International
509	Lecture	University of Milano - Bicocca	Traumatic brain injury 2020: extracranial complications: impact on outcome	13/11/2020	e-SMART 31° SMART VIRTUAL	Scientifc Community		International
510	Oral presentation to a scientific event	ICL	AI in Radiology: The Story Behind the Data	18/11/2020	Virtual IPEM Workshop	Scientific Community	100	National
511	Webinar	University of Cambridge	Current status of multimodality monitoring in TBI	20/11/2020	Online	Scientific Community, Clinicians	Unkown (online)	International
512	Oral Presentation (online)	University Hospital Antwerp	CENTER-TBI: a large scale European Observational Study	23/11/2020	IV International Peruvian Congress of Neurocritical Care	Scientific Community	unknown	International
513	Oral Presentation (online)	University Hospital Antwerp	The CENTER-TBI study	05/12/2020	Virtual ICRAN 2020	Scientific Community	unknown	International
514	Webinar	University of Cambridge	TBI registries	05/12/2020	Online	Scientific Community, Clinicians	Unkown (online)	International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
515	Oral presentation to a scientific event	University of Cambridge	The 2021 Dr Malathi Memorial Oration: Rational approaches to the critical care management of traumatic brain injury	24/01/2021	Online	Scientific Community, Clinicians	Unknown (online)	International
516	Oral Presentation (online)	UMG	Close Out Meeting Center-TBI/Virtuel (Outcome after TBI: Center-TBI Experiences and Results.)	01/02/2021	Antwerp, Belgium	CenTER TBI collaborators	250	international
517	Oral presentation to a scientific event	University of Sheffield	Registry Update	01/02/2021	Close out Meeting	Scientific Community	unknown	International
518	Oral presentation to a scientific event	University of Stirling	Cognitive performance and function after TBI	02/02/2021	Close-out Meeting	Scientific Community	200	International
519	Poster	University Hospital Heidelberg	Injury mechanisms and severity in pediatric traumatic brain injury patients admitted to the ward or intensive care unit: A CENTER-TBI study	07/02/2021	Online (INTS 2021, Melbourne, Australia)	Scientific Community	unknown	International
520	Poster	University Hospital Heidelberg	Outcome prediction of the pressure reactivity index (PRx) and long pressure reactivity index (LPRx) in TBI patients: A CENTER-TBI study	07/02/2021	Online (INTS 2021, Melbourne, Australia)	Scientific Community	unknown	International
521	Oral presentation to a scientific event	University of Cambridge	The emerging science and art of precision medicine in TBI care – lessons from InTBIR	07/02/2021	Online	Scientific Community, Clinicians	Unknown (online)	International
522	Oral presentation	University of Cambridge	Spatial and temporal pattern of ischaemia and abnormal vascular function following TBI	11/02/2021	Melbourne, Australia	Scientific Community, Clinicians	500	International (virtual)
523	Oral presentation to a scientific event	University of Cambridge	Invited Speaker: Advanced imaging in TBI, International Neurotrauma Symposium	11/02/2021	Melbourne, Australia (Virtual)	Scientific Community, Clinicians	Unkown (online)	International
524	Oral presentation to a scientific event	University of Cambridge	Ultra-early versus early magnetic resonance imaging for mild traumatic brain injury: a CENTER-TBI study	11/02/2021	Melbourne, Australia (Virtual)	Scientific Community, Clinicians	Unkown (online)	International
525	Webinar	University of Cambridge	Concussion	01/03/2021	Cambridge	Public	Unkown (online)	National
526	Oral presentation to a scientific event	University of Cambridge	Neuroanatomical Substrates and Symptoms Associated With Magnetic Resonance Imaging of Patients With Mild Traumatic Brain Injury	01/03/2021	Lund, Sweden	Scientific Community, Clinicians	Unkown (online)	International
527	Lecture	University of Milano - Bicocca	Center TBI	04/03/2021	III CONINI - INTERNATIONAL CONGRESS OF NEUROINTENSIVE CARE 2021	Scientifc Community		International

NO.	Type of activities	Main leader (Institution)	Title[2]	Date/Period	Place	Type of audience [3]	Size of audience	Countries addressed
528	Poster	University Hospital Heidelberg	Relationship between intracranial lesions on brain computed tomography and global functional outcome in adolescents with mild traumatic brain injury	04/03/2021	Online (UK Brain Conference 2021)	Scientific Community	unknown	International
529	Poster	University of Cambridge	Communication & Information In The Injured Brain	04/03/2021	Online	Scientific Community	Unkown (online)	International
530	Oral presentation	University of Cambridge	Functional MRI for Diagnosis & Prognosis in Mild Traumatic Brain Injury	05/03/2021	Online	Scientific Community	Unkown (online)	National
531	Lecture	University of Milano - Bicocca	CENTER TBI: Lessons to learn	14/04/2021	EURONEURO	Scientifc Community		International
532	Poster	University of Cambridge	The Lower Limit of Reactivity as an individualized Cerebral Perfusion Pressure target in Traumatic Brain Injury: A CENTER-TBI High-Resolution Sub-Study Analysis	14/04/2021	Online	Scientific Community, Clinicians	Unknown (online)	International
533	Oral presentation to a scientific event	University of Cambridge	Towards autoregulation-oriented management after Traumatic Brain Injury: increasing the accuracy of the CPPopt algorithm.	22/04/2021	Online	Scientific Community, Clinicians	Unknown (online)	International
534	Oral presentation to a scientific event	University Hospital Heidelberg	Mechanisms and severity of traumatic brain injury in pediatric patients admitted to the ward or intensive care unit: Data from the CENTER-TBI study	21/06/2021	Online (Annual meeting nof the German Society of Neurosurgery 2020)	Scientific Community	unknown	National
535	Oral presentation to a scientific event	University Hospital Heidelberg	Does concomitant spine injury in patients with traumatic brain injury affect the outcome?	04/09/2021	Mainz, Germany	Scientific Community	unknown	National
536	Oral presentation at scientific event	LUMC	Dilemmas in very severe traumatic brain injury & informed consent in TBI emergency research	28/04/2021	Online	Online event	150	International
537	Oral presentation educational	LUMC	Traumatic brain injury	04/05/2021	Online	Online	60	National

2.2 Exploitable foreground and plans for exploitation

The integrated research of CENTER-TBI has the potential for high translational impact at both the level of policymakers and health care professionals. We aimed to improve the understanding and care delivery for TBI, with the ultimate goal of improving outcome for patients. The project is built upon a philosophy of collaboration and data sharing in the widest sense. As such, we did not directly aim for exploitation of products resulting from the project and beneficiaries were committed to maximize the benefits of the results of this project funded by public money by facilitating access to the data and broad use of the results.

One of the more tangible products of CENTER-TBI was the development of an open-source database of clinical data and neuroimaging and biomarker results based on Common Data Elements (CDEs). It was agreed that this product should be made available to the community. Whilst adhering to FAIR principles, we wish to ensure "good use" of the data, and have therefore implemented a study- and publication proposal platform (for details see section 1.4.6), and require signing of a data use agreement prior to providing external researchers access to the data.

The foreground and plans for exploitation identified by CENTER-TBI beneficiaries are listed in Section 2.2.2.

2.2.1 List of applications for patents, trademarks, registered designs, etc…

There were no applications to report.

2.2.2 List and description of exploitable foreground

Type of exploitable foreground	Description of exploitable foreground	Confidential (YES/NO)	Foreseen embargo date dd/mm/yyyy	Exploitable product(s) or measure(s)	Sector(s) of application [1]	Timetable, commercial or any other use	Patents or other IPR exploitation (licences)	Owner & other beneficiary(s) involved
Commercial exploitation of R&D results	Software for brain lesion detection	NO	n/a	BLAST-CT	Healthcare, diagnostics	Next five years	n/a	ICL / University of Cambridge
Commercial exploitation of R&D results	Software for brain (lesion) quantification	YES	n/a	icobrain ct (tbi)	Healthcare, diagnostics	for commercial use available	n/a	icometrix

3 Report on societal implications

Table 8: Report on societal implications

A General Information	
Grant Agreement Number:	602150
Title of Project:	Collaborative European NeuroTrauma Effectiveness Research in TBI
Name and Title of Coordinator:	Prof. Tomas Menovsky – Antwerp University Hospital

B Ethics	
1. Did your project undergo an Ethics Review (and/or Screening)? If Yes: have you described the progress of compliance with the relevant Ethics Review/Screening Requirements in the frame of the periodic/final project reports? Yes. Five ethics related deliverables were delivered during the course of the project (D1.02, D16.01, D16.02, D16.03 and D16.04). Their submission was reported in the relevant periodic reports. Sections 1.3.2 and 1.3.3 of the final report also details how the collection of clinical and epidemiological data was done in strict accordance with EU law as far as ethics, privacy and data protection are concerned.	**Yes**
2. Please indicate whether your project is involved any of the following issues (tick box) :	**Yes**
Research on Humans	
• Did the project involve children?	Yes
• Did the project involve patients?	Yes
• Did the project involve persons not able to give consent?	Yes
• Did the project involve adult healthy volunteers?	Yes
• Did the project involve Human genetic material?	Yes
• Did the project involve Human biological samples?	Yes
• Did the project involve Human data collection?	Yes
Research on Human embryo/foetus	
• Did the project involve Human Embryos?	No
• Did the project involve Human Foetal Tissue / Cells?	No
• Did the project involve Human Embryonic Stem Cells (hESCs)?	No
• Did the project on human Embryonic Stem Cells involve cells in culture?	No
• Did the project on human Embryonic Stem Cells involve the derivation of cells from Embryos?	No
Privacy	
• Did the project involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	Yes
• Did the project involve tracking the location or observation of people?	No
Research on Animals	
• Did the project involve research on animals?	No
• Were those animals transgenic small laboratory animals?	No
• Were those animals transgenic farm animals?	No

• Were those animals cloned farm animals?	No
• Were those animals non-human primates?	No
Research Involving Developing Countries	
• Did the project involve the use of local resources (genetic, animal, plant etc)?	No
• Was the project of benefit to local community (capacity building, access to healthcare, education etc)?	No
Dual Use	
• Research having direct military use	No
• Research having the potential for terrorist abuse	No

C Workforce Statistics

3. Workforce statistics for the project: Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Type of Position	Number of Women	Number of Men
Scientific Coordinator	11	21
Work package leaders	10	19
Experienced researchers (i.e. PhD holders)	33	57
PhD Students	34	40
Other	61	41

4. How many additional researchers (in companies and universities) were recruited specifically for this project?	**44**
Of which, indicate the number of men:	23

D Gender Aspects

5. Did you carry out specific Gender Equality Actions under the project? No

6. Which of the following actions did you carry out and how effective were they? Not applicable

	Not effective at all				Very effective
❑	Design and implement an equal opportunity policy	○	○	○	○	○
❑	Set targets to achieve a gender balance in the workforce	○	○	○	○	○
❑	Organise conferences and workshops on gender	○	○	○	○	○
❑	Actions to improve work-life balance	○	○	○	○	○
❑	Other:					

7. Was there a gender dimension associated with the research content – i.e. wherever people were the focus of the research as, for example, consumers, users, patients or in trials, was the issue of gender considered and addressed?

No

E Synergies with Science Education	
8. Did your project involve working with students and/or school pupils (e.g. open days, participation in science festivals and events, prizes/competitions or joint projects)?	
Yes- please specify :	• Scholarship programs • Courses/trainings in Systematic reviews
9. Did the project generate any science education material (e.g. kits, websites, explanatory booklets, DVDs)?	
No	

F Interdisciplinarity	
10. Which disciplines (see list below) are involved in your project?	
⊙	Main discipline: 3.2 Clinical medicine
⊙	Associated discipline:N/A

G Engaging with Civil society and policy makers		
11a. Did your project engage with societal actors beyond the research community? (if 'Yes/No', go to Question 14)	No	
11b. If yes, did you engage with citizens (citizens' panels / juries) or organised civil society (NGOs, patients' groups etc.)?		
⊙	Yes/No	
○	Yes- in determining what research should be performed	
○	Yes - in implementing the research	
○	Yes, in communicating /disseminating / using the results of the project	
11c. In doing so, did your project involve actors whose role is mainly to organise the dialogue with citizens and organised civil society (e.g. professional mediator; communication company, science museums)?	○ ○	Yes No
12. Did you engage with government / public bodies or policy makers (including international organisations)		
○	Yes/No	
○	Yes- in framing the research agenda	
○	Yes - in implementing the research agenda	
⊙	Yes, in communicating /disseminating / using the results of the project	
13a. Will the project generate outputs (expertise or scientific advice) which could be used by policy makers?		
○	Yes – as a **primary** objective (please indicate areas below- multiple answers possible)	
⊙	Yes – as a **secondary** objective (please indicate areas below - multiple answer possible)	
○	Yes/No	

13b. If Yes, in which fields?					
Energy		Regional Policy		Research and Innovation	
Transport					

13c. If Yes, at which level?	
○	Local / regional levels
○	National level
○	European level
⊙	International level

H Use and dissemination	
14. How many Articles were published/accepted for publication in peer-reviewed journals?	216[1]

[1] Some discrepancy exists between the number of publications in the report and on the portal as some publications could not be entered as the Journal was not yet referenced.

To how many of these is open access provided?	151
How many of these are published in open access journals?	142
How many of these are published in open repositories?	97
To how many of these is open access not provided?	58
Please check all applicable reasons for not providing open access:	
☑ publisher's licensing agreement would not permit publishing in a repository ☑ no suitable repository available ☑ no suitable open access journal available ☑ no funds available to publish in an open access journal ☑ lack of time and resources ☑ lack of information on open access ❑ other: ……	
15. How many new patent applications ('priority filings') have been made? *("Technologically unique": multiple applications for the same invention in different jurisdictions should be counted as just one application of grant).*	0

16. Indicate how many of the following Intellectual Property Rights were applied for (give number in each box).	Trademark	0
	Registered design	0
	Other	0

17. How many spin-off companies were created / are planned as a direct result of the project?	3
Indicate the approximate number of additional jobs in these companies:	3

18. Please indicate whether your project has a potential impact on employment, in comparison with the situation before your project:

❑	Increase in employment, or	❑	In small & medium-sized enterprises
❑	Safeguard employment, or	❑	In large companies
❑	Decrease in employment,	☑	None of the above / not relevant to the project
☑	Difficult to estimate / not possible to quantify		

19. For your project partnership please estimate the employment effect resulting directly from your participation in Full Time Equivalent (*FTE = one person working fulltime for a year*) jobs:	*Indicate figure:* **11**
Difficult to estimate / not possible to quantify	☑

I Media and Communication to the general public

As part of the project, were any of the beneficiaries professionals in communication or media relations?

No

21. As part of the project, have any beneficiaries received professional media / communication training / advice to improve communication with the general public?

No

22. Which of the following have been used to communicate information about your project to the general public, or have resulted from your project?

☑	Press Release	☑	Coverage in specialist press
☑	Media briefing	☑	Coverage in general (non-specialist) press
☑	TV coverage / report	☑	Coverage in national press
☑	Radio coverage / report	☑	Coverage in international press
☑	Brochures /posters / flyers	☑	Website for the general public / internet
☑	DVD /Film /Multimedia	☑	Event targeting general public (festival, conference, exhibition, science café)

23. In which languages are the information products for the general public produced?

☑	Language of the coordinator	☑	English
☑	Other language(s):	Slovak, Hungarian, French, Italian, Norwegian, Chinese, German	

4 Final report on the distribution of the European Union financial contribution

To be completed during the second delivery of the final report, once the remaining EC contribution has been paid out and distributed.