Collaborative **RE**search on **AC**ute **T**raumatic brain **I**njury in intensi**V**e care medicine in Europe

Prospective longitudinal data collection and Comparative Effectiveness Research (CER) for traumatic brain injury (TBI)

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Beneficiaries:

Country	Name	Acronym
ITALY	Italian Group for the Evaluation of Interventions in Intensive Care Medicine	NEGRI
HUNGARY	Magyar Honvedseg Egeszsegugyi Kozpont	MHEK
POLAND	Warszawski Uniwersytet Medyczny	MUW
SLOVENIA	Splosna Bolnisnica Novo Mesto	SBNM
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CYPRUS	Edex-Educational Excellence Corporation Limted	University of Nicosia Medical School
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GREECE	Panepistimiako Geniko Nosokomeio Irakleiou	PEPAGNH
ITALY	Orobix Srl	OROBIX

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1. Executive summary

Traumatic brain injury (TBI) is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force. It is a leading cause of death and disability and the main cause of death among the under-45s.

TBI can be classified as mild, moderate, and severe. Mild TBI is variably managed but most moderate and almost all severe TBI patients who manage to reach a hospital are admitted to an intensive care unit (ICU). Although these patients represent only 20% of the total, they carry the main burden of the disease. Hence, the ICU is ideally placed to adequately evaluate and monitor the bulk of the burden of TBI, identify and assess the most effective clinical interventions, and recognize excellence in patient management. Some permanent disability is estimated to occur in 10% of mild, 66% of moderate, and 100% of severe TBIs. Estimated in-hospital mortality is <5% in mild TBI, while it increases to approximately 20% in moderate, and approximately 45% in severe cases at six months.

In the past, research into the epidemiology of TBI, its impact on medium- and long-term patient outcomes, and the variability of treatment approaches were far from satisfactory. The International Initiative for Traumatic Brain Injury Research (InTBIR) collaborative effort, formed by the US National Institutes of Health, Canadian Institutes of Health Research and the European Commission, sought to overcome this problem by launching an initiative to harmonize data collection at European and North American level through the creation of patient registries based on common data elements.

The CREACTIVE Consortium, coordinated by GiViTI (Italian Group for the Evaluation of Interventions in Intensive Care Medicine), proposed to contribute to the global InTBIR collaborative effort by conducting a prospective, longitudinal, non-randomised clinical study on TBI patients in 6 members states (Cyprus, Greece, Hungary, Italy, Poland, Slovenia) and Israel, in the specific area of moderate to severe TBI in the critical care setting.

The main study objectives were to consolidate a network based on the existing PROSAFE ICU consortium; set up a database to collect data on moderate to severe TBI patients; reach a consensus on the CDEs to be collected in CREACTIVE; establish biological and imaging repositories to store and analyse samples and CT and MRI scans from a subset of TBI patients, with a view to identifying prognostic markers of TBI complications and outcome; describe the epidemiology of moderate to severe TBI in 7 countries; build a prognostic model based on appropriate short- and long-term outcome measures; explore the most effective clinical interventions for optimally treating TBI patients; identify determinants of optimal vs. suboptimal performance; promote data sharing with other InTBIR consortia.

Between March 2014 and March 2019, valid, superior quality data was collected by 81 ICUs on 7910 TBI patients (7307 adults and 603 children), in addition to biological samples from over 2000 patients and CT and MRI scans from over 1300. Outcome assessment by telephone was performed at 6 months in all patients and at 12 months in a subset. At 31 March, 2019 medium-term outcome data were available on approximately 5,800 patients.

Overall the study fulfilled its ambitions and has made a solid contribution to the success of the InTBIR initiative to combine forces to improve outcomes and lessen the global burden of traumatic brain injury by 2020.

2. Description of the project context and the specific objectives

Traumatic brain injury (TBI) is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force [1]. It is a leading cause of death and disability and the main cause of mortality among the under-45s. About 50% of the global population are directly affected by TBI on one or more occasion over their lifetime and it costs the world economy an estimated $US400 billion per year [2]. TBI can be classified into mild, moderate, and severe, based on assessment of the level of coma, loss or alteration of consciousness, duration of post-traumatic amnesia, and neuroimaging results [3].

While mild TBI patients are variably managed in the different health services, most moderate and almost all severe TBI patients who manage to reach a hospital are admitted to an intensive care unit (ICU). Although these patients represent only 20% of the total, they carry the main burden of the disease and some permanent disability is estimated to occur in 10% of mild, 66% of moderate, and 100% of severe TBIs. Estimated in-hospital mortality is <5% in mild TBI, while it increases to 21% in moderate, and 46% in severe cases at six months. Hence, the ICU is in an ideal position to adequately evaluate and monitor the bulk of the burden of the disease, explore the most effective clinical interventions, and recognize excellence in TBI management. Moreover, even mild TBI patients can be admitted to ICUs in cases of accompanying conditions (polytrauma, organ failure, important comorbidity, etc.).

Until recently, research into the epidemiology of TBI, its impact on medium- and long-term patient outcomes, and the variability of treatment approaches were far from satisfactory. Data included in existing registries were collected from highly specialised care facilities, with vast differences in research methods and formatting of information [4,5]. This scenario meant, on the one hand, that data did not reflect the complete picture, as a great proportion of TBI patients were usually admitted to non-specialized centres and, on the other, it precluded the possibility to meaningfully utilize and analyse collected data.

Data harmonisation and TBI patient coverage

The International Initiative for Traumatic Brain Injury Research (InTBIR) collaborative effort, formed by the US National Institutes of Health (NIH), the Canadian Institutes of Health Research and the European Commission, sought to overcome this problem by launching an initiative to harmonize data collection at European and North American level through the creation of patient registries based on common data elements (see https://www.commondataelements.ninds.nih.gov/TBI.aspx#tab=Data_Standards).

The CREACTIVE Consortium, coordinated by GiViTI (Italian Group for the Evaluation of Interventions in Intensive Care Medicine), proposed to contribute to the global InTBIR collaborative effort by conducting a prospective, longitudinal, non-randomised clinical study on TBI patients, collecting data of the highest quality in 6 members states (Cyprus, Greece, Hungary, Italy, Poland, Slovenia) and Israel, in the specific area of moderate to severe TBI. Data would be gathered not only from highly specialized facilities, as this would have introduced an important selection bias, but also from adult and paediatric ICUs in small peripheral, regional referral, teaching and non-teaching hospitals, thus covering the whole spectrum of facilities caring for patients with moderate to severe TBI of all ages. CREACTIVE was built on the long experience of GiViTI, dating back to 1991, and the previous work of the well-established EU-funded ICU network PROSAFE, whose mission was and remains to promote patient safety and quality of care improvement. The symbol of the PROSAFE consortium is the daisy (composed of a Core and Petals). The members collect Core data on all critically ill patients admitted to the ICU but the software is designed to add “Petals”, or data subsets, to the Core. The network developed a TBI “Petal” and established the CREACTIVE study. Collection is envisaged to continue beyond the life of the study funding period.

Patient-centered outcome measures

From the patient perspective, given the importance of TBI-related disabilities, mortality could not be considered the only outcome by which to assess the impact of the condition. To better assess outcome in this

field and complete the picture, measures not only of mortality but also of injury-related disabilities needed to be taken into account, through performance of a follow-up assessment at 6 months from trauma. The CREACTIVE consortium tasked itself with setting up a multidisciplinary follow-up advisory board to define the qualitative assessment to be performed at six months and to select the CDEs to be collected. Patient follow-up was not part of routine practice in the vast majority of the participating centres, but required mobilization of specific resources. The goal was to collect defined qualitative and quantitative follow-up data in each country using the most appropriate healthcare provider (according to patient type and age).

Inclusion of children and their specific follow up needs

Children were deemed to deserve specific consideration being especially vulnerable to such injury due to their inherited anatomic and physiological characteristics. Moreover, infants' and children's developing brains respond differently than adults to TBI. Protocols and modalities used to in the treatment of moderate to severe paediatric TBI patients are mostly extrapolated from adult patient studies or "expert opinion", while scientifically-based data is lacking. Post TBI outcome measures are also difficult to assess in this age group. Most functional and cognitive tools used to evaluate outcome post TBI need patient cooperation. This can pose problems in children and relies mainly on third party information (from parents, caregivers, teachers, etc.). The quality of the data of these tools varies among age groups and studies, questioning their validity. Adding an objective, quantitative and holistic measurement to the current tools was considered to be very helpful. The CREACTIVE study provided a unique opportunity to explore sleep and other neurocognitive disturbances post TBI that affected children and to correlate these results with the epidemiological and clinical baseline and post TBI outcomes.

Development of reliable prognostic models to explore the effectiveness of clinical interventions and identify excellence and best practices.

In non-randomized studies, the use of crude data to compare outcomes among subgroups (e.g. patients receiving or not receiving specific interventions, admitted to one centre rather than another) is biased by the presence of confounders [6]. For example, in everyday life, patients who receive a specific treatment differ from those who do not, due to treatment indications, physician choices, resource availability, and other factors. To sensibly compare outcomes in non-randomized studies it becomes mandatory to adjust for all these confounders [6].

In the critical care medicine field, mortality is typically used as the main outcome indicator. At the start of the project, the prognostic models of mortality that had been developed over the preceding thirty years for adjusting purposes presented a series of problems. First, a scoring system developed in a specific geographic, economic and social context produces biased mortality estimates when applied to other areas. Second, the development of prognostic models is so complicated that once developed, they tend not to be updated for many years, generating a temporal bias related to the improvement of health care quality and changes in case-mix over time, which the model cannot account for [7]. Lastly, the internal validity of currently used severity scores has never been adequately tested in important subgroups and so miscalibration of the model could not be ruled out [7], compromising their predictive power.

Prior to CREACTIVE, the PROSAFE consortium had sought to overcome these problems by: developing a prognostic model that took into account the resources available in the ICU in general (e.g. doctor to patient ratio; bed occupancy rate; GDP parity purchase power) together with patient conditions (e.g. comorbidities, Glasgow Coma Scale, organ failures, physiological derangement) thus greatly limiting the context-sensitive variable bias; creating a new model every year, thus avoiding the temporal bias; generating a model that calibrated well, overall and in each subset identified by the variables included in the model (e.g. septic shock, surgical status, gender). This was obtained using a statistical tool created ad hoc: the GiViTI calibration belt [8]. The goal was to apply this state-of-the-art approach to TBI. Furthermore, to better assess outcome in this field, measures not only of mortality but also of disability were to be taken into account through the follow-up assessment at 6 months from trauma.

The effectiveness of clinical interventions to treat TBI.

The main goals in managing patients with moderate to severe TBI are to (a) maintain life in spite of primary tissue injury, (b) protect the brain from secondary neuronal injury, and (c) prevent secondary injury in other organs resulting in multiorgan dysfunction syndrome [1]. The pathophysiological mechanisms that affect the outcome of these patients include brain oedema, increased intracranial pressure, hyper- and hypotension, hypoxia, brain ischaemia, hypercapnia, hyper- and hypoglycaemia (peripheral or regional), hyper- and hyponatraemia, seizures, sepsis, etc. A number of interventions designed to manage these derangements were and continue to be a topic of controversy, mainly due to the lack of high quality randomised-controlled trials (RCTs).

The goal of CREACTIVE was to analyse the data collected in the CREACTIVE registry to offer insights into different interventions, as use of intracranial pressure monitoring, performance of decompressive craniectomy, and rehabilitation timing.

Identification of excellent and suboptimal ICUs to ascertain and share best practices.

One of the most widely used indicators in quality-of-care-assessment literature is the standardised mortality ratio (SMR), i.e. the ratio between observed and expected mortality in a subgroup, according to the benchmark [6]. When a prognostic model is used as benchmark for the centres on which it is based, the SMRs of the individual centres become distributed around 1 but some exhibit a statistically significant deviation from 1. This means that their better- or worse-than benchmark outcome is due not to chance variation but to potentially different performance. Moreover, SMRs that do not deviate significantly from 1 may hide statistically significant differences from benchmark in specific classes of risk (say, patients at low risk of death), or in specific subgroups (say, patients with intraparenchymal haemorrhage). The CREACTIVE Consortium planned to use the in-house GiViTI calibration belt to identify centres with the highest performance in TBI treatment and those with poor results. First, by singling out the features (e.g. ICU or hospital organization, existence of high-level specific skills) that determine the high quality results of the best centres. Second, by promoting collaboration among high-performing ICUs and those needing to improve their expertise in TBI. CREACTIVE aimed to achieve this goal also through targeted educational campaigns and fellowships to exchange best practices.

Weighting the prognostic importance of circulating and imaging biomarkers.

The damage occurring after trauma is the consequence of primary and secondary injury [8]. Whilst the first is directly caused by the impact, the second is governed by a complex set of cellular processes and biochemical cascades that occur in the minutes to days following TBI. Through different pathways, the most critical results of secondary injury are progression of the haemorrhagic lesion and/or cytotoxic and vasogenic oedema (swelling of the brain), which ultimately cause a rise in intracranial pressure. Since this accounts for the greatest number of TBI-related hospital deaths [8], the main aim of treatment in the acute stage of TBI is to control and lower intracranial hypertension [9].

This prompted the need to better characterise the progression of haemorrhagic lesions and cerebral oedema and to increase knowledge on factors that can influence them. CREACTIVE proposed to study the evolution of focal lesion volume progression (haemorrhagic and/or perilesional oedema) through the analysis of serial computed tomography (CT) and magnetic resonance (MR) images and circulating and cerebrospinal fluid biomarkers. Despite the increasing volume of evidence highlighting the association between outcome and CT and MR imaging [10] and circulating biomarkers [11], these important aspects had previously always been analysed independently from each other, and never collected together in the same population.

This constituted the rationale for implementing centralised repositories of detailed clinical data, biological samples (biobank), and repeated clinical imaging, on a subset of adult patients (up to 2,000), providing a unique opportunity for integrated analysis of secondary injury following TBI. The plan was to evaluate the variability in the progression of both the haemorrhagic lesion and the perilesional oedema, starting from automated analysis of imaging data, and to assess their association with outcome. The analysis would then concentrate

on circulating biomarkers. It was planned to assay biomarkers already postulated to potentially have a role in the prognosis of TBI (neuron specific enolase [NSE], as a marker of neuronal damage; S100 calcium binding protein B [S100B], as a marker of glial damage; neurofilaments [NFL] (as a marker of axonal injury) in order to validate them for the first time on a large sample, which had not previously been done, in addition to other specific markers, as the highly innovative marker pentraxin-3 (PTX-3). The goal was to collect samples at ICU admission, at day 5 after admission and, in a subset of patients admitted to longer-term follow up, at 12 months after the TBI. Given the complexity of the entire picture and the expected new knowledge that could potentially be available when the samples were ready for analysis, it was planned to set up an ad hoc, independent scientific advisory board (SAB) to finalize the protocol of the various determinations. Depending on the results of the imaging analysis and the new available evidence, the SAB would jointly identify which already recognized circulating and CSF biomarkers, and which other innovative ones would be tested.

Promoting data sharing within the European consortia of InTBIR.

CREACTIVE, in collaboration with the European Commission-funded Human Brain Project/Medical Informatics Platform (HBP/MIP), was tasked with promoting implementation of a federated data-sharing platform among the European members of InTBIR.

The specific objectives of the CREACTIVE study were to:

- consolidate a network based on the existing PROSAFE consortium in order to set up a database to collect data on moderate to severe TBI patients;
- join forces in the fields of data harmonisation and data sharing with the International Initiative for Traumatic Brain Injury Research (InTBIR);
- establish biological and imaging repositories to store and analyse samples and CT and MRI scans from a selected subset of TBI patients, with a view to exploring prognostic markers of TBI complications and outcome;
- describe the epidemiology of moderate to severe TBI in 7 countries;
- build a prognostic model based on appropriate short- and long-term outcome measures;
- explore the most effective clinical interventions for optimally treating TBI patients;
- identify determinants of optimal vs. suboptimal performance;
- promote data sharing within the European consortia of InTBIR.

References

1. Maas, A.I., N. Stocchetti, and R. Bullock, *Moderate and severe traumatic brain injury in adults.* Lancet Neurol, 2008. **7**(8): p. 728-41.
2. Maas AIR, Menon DK et al., *Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research*. Lancet Neurol. 2017 Dec;16(12):987-1048.
3. Saatman, K.E., et al., *Classification of traumatic brain injury for targeted therapies.* J Neurotrauma, 2008. **25**(7): p. 719-38.
4. Maas, A.I., *Standardisation of data collection in traumatic brain injury: key to the future?* Crit Care, 2009. **13**(6): p. 1016.
5. Maas, A.I., et al., *Re-orientation of clinical research in traumatic brain injury: report of an international workshop on comparative effectiveness research.* J Neurotrauma, 2012. **29**(1): p. 32-46.
6. Rothman, K.J., S. Greenland, and T.L. Lash, *Modern Epidemiology*. Second edition ed. 2008, Philadelphia, PA: Lippincott Williams & Wilkins.

7. Poole, D. and G. Bertolini, *Outcome-based benchmarking in the ICU Part II: Use and limitation of severity scores in critical care*, in *Patient Safety and Quality of Care in Intensive Care Medicine*, J.-D. Chiche, et al., Editors. 2009, MWV: Berlin. p. 151-159.
8. Ghajar, J., *Traumatic brain injury.* Lancet, 2000. **356**(9233): p. 923-9.
9. Farahvar, A., et al., *Response to intracranial hypertension treatment as a predictor of death in patients with severe traumatic brain injury.* J Neurosurg, 2011. **114**(5): p. 1471-8.
10. Hunter, J.V., et al., *Emerging imaging tools for use with traumatic brain injury research.* J Neurotrauma, 2012. **29**(4): p. 654-71.
11. Hergenroeder, G.W., et al., *Biomarkers in the clinical diagnosis and management of traumatic brain injury.* Mol Diagn Ther, 2008. **12**(6): p. 345-58.

3. Description of the main S & T results/foregrounds

The CREACTIVE observational clinical study is registered in the ClinicalTrials.gov registry with the following identifier: **NCT02004080**

The link to the registry is as follows: http://www.clinicaltrials.gov.

All ICUs collecting data for the CREACTIVE project received the prior approval of the respective local Ethics Committees.

3.1 Scientific management and coordination of the project

The main objective of Work Package 1 was to set up an effective management and coordination framework for the consortium to ensure the correct progress of the project towards its planned scientific and technical objectives, based on smooth and efficient communications and coordination of all partners involved. The work package was led by the Coordinator, NEGRI.

The coordinator also liaised with and actively participated in the InTBIR Initiative (EU, NIH, DoD CIHR) with a view to promoting data sharing across the wider network

3.2 Developing the CREACTIVE case report form

Work package 2, led by BGU, was devoted to developing the Case Report Form in which to collect the TBI, after reaching a consensus on the common data elements to be included. Work started with a review of the TBI petal developed under the PROSAFE project, which was adapted to achieve compliance with the data standards endorsed by the InTBIR initiative. This renders the data collected by the CREACTIVE consortium usable by the wider InTBIR network in large prospective clinical studies designed to identify the most effective clinical treatments for TBI.

The CREACTIVE electronic Case Report Form (eCRF) was a TBI module of the basic PROSAFE eCRF. The data included demographics, comorbidities, location of the patient before admission, reasons for admission, surgical status, diagnoses on admission, severity of infection on admission if present, Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment score (SOFA) variables, failures and complications occurring during the stay, severity of infection if any, major procedures and interventions, ICU- and hospital outcomes.

The CRF included all core InTBIR TBI-CDEs. An assessment was made of additional variables to be collected with a view to achieving the project aims. Particular attention was paid both to the inclusion of prognostic factors and to the collection of data on medium-term disabilities.

3.3 Systems implementation, localisation and maintenance

The purpose of WP3, led by Orobix, was to develop the IT systems and software required to gather data on TBI patients admitted to ICUs and to implement the various supporting and monitoring systems needed to accompany data collection.

The following systems and tools were developed:

CREACTIVE electronic Case Report Form (eCRF)

This was a module of the PROSAFE eCRF. The software was developed to ensure the anonymous transfer of patient data, permitting only the ICU transmitting the data to have access to sensitive patient information. CREACTIVE incorporated a series of approximately 590 congruency checks to ensure the high quality of stored data. Furthermore, throughout the life of the project, the CRF was continuously improved and updated, to accommodate emerging problems and needs. System bugs were dealt with as they appeared. All new versions of the eCRF that modify the dataset were released to be ready for use as from January of each year with a view to including the same data elements for periods of one year at least. Releases of revised software started with a pilot period involving a restricted group of users. Once all the tests had been passed, the release became available to all project participants.

Web-based systems

Several systems were developed to handle debugging procedures, plan overall eCRF development, manage the registration of ICUs into the project, and centrally monitor their participation in the study. A web-based statistical analysis system (the Analyser) was also developed to be used by participants to analyse own data and compare them with the entire dataset.

Each participating ICU was requested to provide a detailed structural description of the ICU facility at registration, which was required to be reviewed and revised on a yearly basis. Information was requested on logistics, organization and resource availability. This information was used for data analysis, to assess the extent to which these variables influenced final patient outcomes. The information was managed via a web-based registration system supervised by NEGRI. The system, developed ad hoc and localised in the various consortium languages, also permitted real-time monitoring of ICU participation in terms of patient recruitment and data quality since data were synchronized twice a day for each centre.

CREACTIVE Translation Manager

The various systems were localized into 6 languages: English, Greek, Hungarian, Italian, Polish, and Slovenian, following a stringent back-translation procedure to ensure exact correspondence of terms, using the specially designed CREACTIVE Translation Manager.

Imaging data collection infrastructure

The imaging biobank was developed by Orobix and deployed on infrastructure provided by NEGRI. A user-side application was developed for retrieval, review, annotation de-identification/anonymisation and collection of medical imaging data. The application securely connected to the imaging biobank.

Centres participating in the imaging sub-study were supported in the collection of data and images through the in-house DICOM.Next software. The software is designed to visualize CT series, annotate intraparenchymal lesions, input subject-specific data (including the CREACTIVE ID for the participant) and automatically anonymise and send the series to the server infrastructure hosted at partner NEGRI. Support for set-up, use and maintenance of the software as well as data extraction and data quality evaluation was provided by Orobix.

In the final year, the number of series with manually annotated intraparenchymal lesions became sufficient for training automated lesion identification methods. Manual annotation by the investigators prior to data upload was therefore no longer required for the remainder of the project. This led to a marked increase in the number of series collected in the final imaging dataset.

The dataset is quality controlled and will made available through the project’s data sharing policy.

Collaboration with the Human Brain Project / Medical Informatics Platform team (HBP/MIP)

To promote InTBIR's data sharing efforts, the CREACTIVE consortium started a collaboration in 2016 with the Medical Informatics Platform (MIP) team of the Human Brain Project (HBP), the aim being to develop and pilot a federated, web-based data-sharing platform on which to run analyses and algorithms on combined

data for simple statistics purposes, starting with CREACTIVE data. NEGRI adapted the Calibration Belt and Calibration Test analyses already created by its team of statisticians for CREACTIVE purposes to enable it to be performed on the Algorithm Factory of the MIP. NEGRI developed a distributed version of these algorithms to validate prognostic models on federated database. The algorithms were implemented in R language and tested on NEGRI's servers.

Data definitions were shared with the HBP group. The next step will be to integrate the GiViTI calibration belt code distributed in the MIP code on a test platform simulating several MIP installations. Work to finalize the federated, web-based data-sharing platform will be completed under the Infrastructure Voucher Programme funded by HBP (ending in 31 March, 2020).

3.4 Data collection

Data collection (work package 4, led by MUW) represented the core activity of the project since it was centred on the actual data collection work and related tasks. Patient data were collected during ICU stay, six months after the traumatic event, and 12 months after the TBI in a subset of patients, in seven countries. The work package also envisaged initial and periodic data collector training and organisation of annual meetings to present findings and discuss any collection-related problems that emerged.

The CREACTIVE project's ambition was to create a unique repository of different kinds of data and samples related to a large number of patients with TBI, which will now be made available to the scientific community to perform studies. These data were composed of the clinical characteristics of the patients, the interventions received, the admitting facilities, the different outcomes, brain imaging data, and blood samples collected at two and in some cases three different time points of the acute clinical course. All participating centres received the approval of the respective ethics committee before starting collection.

The Consortium was highly motivated towards data collection because of the added value each ICU received and will in the future continue to receive from comparison of own and average data. The network adopted the PROSAFE programme for data collection on all critical care areas and further developed it for the purposes of the CREACTIVE project. Patient follow-up data was collected on all patients six months after the TBI event. CREACTIVE data collection officially started, in the Reporting Period 1, on 15 March, 2014. **At 31 December, 2018, 7910 patients had been collected with valid data (7307 adults and 603 children).**

The CREACTIVE Consortium collected the core PROSAFE data on all ICU patients, not just patients with TBI. These data included demographics, comorbidities, location of the patient prior to admission, reasons for admission, surgical status, diagnoses at admission, severity of infection at admission, where present; Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment score (SOFA) variables, failures and complications occurring during ICU stay, severity of infection if any, major procedures and interventions, ICU- and hospital outcomes.

There were three main objectives for collecting the core PROSAFE data on all admitted patients. First, to prevent TBI patients from being missed and to monitor that this did not occur, through an automatic alert built into the CRF. This avoided the introduction of selection bias by the investigators. One example is an ICU collecting some admitted patients but omitting others to reduce workload. Second, determining individual ICU performance, not only in TBI management but also in general terms, enabled us to study how the two were correlated and, accordingly, to optimize intervention strategies. For example, evidence indicates that the ICU case mix can have a major impact on performance: ICUs with high volumes of severe patients perform better than other ICUs. Likewise, ICUs with a high volume of severe patients probably also perform better in TBI patients, hence the need to analyse which groups or subgroups of high-volume severe patients influenced performance in TBI (e.g. multiple trauma without TBI) and to include this vital variable in the prognostic model. Third, it was vital to obtain data on staff workload in terms of the complexity of care of the total case mix present in the ICU when the case mix included a TBI patient.

ICU recruitment

The Country Coordinators were tasked with recruiting as many ICUs as possible in their respective country with a view to increasing national representativeness. They were responsible for training providers on correct data collection and for monitoring progress over time, by means of an online ICU monitoring system. It enabled Country Coordinators to check the validity of the data entered by participating ICUs and to monitor the Status levels of the entered patients; it also provided a data validity and monitoring update on the number of ICU admissions, occupancy rate, overall status of PROSAFE (core) and CREACTIVE (specific TBI) data, and details on patient follow up status. It gave various details on the status of the PROSAFE software at each ICU, i.e. the last date the ICU was online; the last date the data were synchronized with the central repository; which version of the software was being used by the ICU (whether it was the latest available or a previous version).

Country	**Total number of recruited (P)ICUs**	**Actual number of (P)ICUs collecting valid data**	**Expected number of recruited (P)ICUs**
Cyprus	4	1	1
Greece	13	5	10
Hungary	13	7	10
Israel	9	2	5
Italy	91	54	80
Poland	27	8	15
Slovenia	19	4	5

At 31 December, 2018, the partners had recruited the above numbers of ICUs to collect data. As the Table shows, many ICUs were recruited but not all continued to collect data throughout the entire project or collected insufficient or low quality data.

Data collectors were provided with update training during the reporting period and new data collectors were trained to gather information in the eCRF. Training in data collection was either through site visits, with the aid of social media (Skype, Team Viewer, e-mails), training days and workshops.

Paediatric ICU recruitment

The paediatric ICUs (PICUs) formed a subset of the total recruited facilities and the related paediatric subproject took the name of ***CREACTKids***. Infants and children are in fact more vulnerable and prone to develop severe head injury from head directed trauma compared to adults. However, children are not small adults and require specific protocols.

Data quality control

A senior intensivist was responsible at each ICU for protocol and data integrity. Being multilingual (English, Greek, Hungarian, Italian, Polish, and Slovenian), investigators entered data into the CREACTIVE eCRF in their own native language, thereby removing any language barriers. Data collectors were provided with detailed definition pop-ups of all items to be collected and a comprehensive, user-friendly, fully indexed, online, operative manual which was accessible during data entry.

A complex, multidimensional validation system ensured maximum data quality. The first level of controls was implemented behind data collection, and followed three different rules: grouping, enabling or disabling, and mutually excluding items. Second level controls were activated during data collection and included:

completeness checks, warnings on borderline values, and errors. As many as 589 distinct cross variable checks were performed: 458 for date inconsistency, 84 for clinical inconsistency, 21 for borderline values, 6 for out-of-range values, and 20 for logical inconsistency. The congruency checks were continuously reviewed and implemented, based on user suggestions, and were of five types: validity (e.g. incorrect date); plausibility (e.g. very high body mass index); logical congruency (e.g. hospital discharge could not precede ICU discharge); clinical congruency (e.g. a patient with ARDS could not have PaO2/FiO2>200); score congruency (e.g. a patient with brain coma could not have Glasgow Coma Scale >8). The system allowed inconsistent or implausible data to be saved but marked the record as problematic.

Each individual unit's data were synchronized with the central GiViTI server every 12 hours and centrally processed, searching for inconsistencies that could not be automatically picked up by the system during data input (e.g. average mortality should not be lower in patients with GCS=3 than in patients with GCS =4-5). A data quality report was produced twice a year and sent to the ICUs with any remaining unsolved queries.

This complex process regulated the "Status" of each patient record, indicating the accuracy level of each individual record (Status 1: Presence of unresolved errors and/or warnings; Status 2: Incomplete data; Status 3: Data complete except for hospital and long-term outcome; Status 4: Data complete and correct; Status 5: Data not complete but the missing data are irretrievable).

To ensure complete patient recruitment, queries were sent to centres with significant heterogeneity in numbers of monthly admissions, assessed using the Chi-square test. Lastly, to avoid selection bias, in each ICU, admissions in months with a percentage of Status 4 patients (complete and consistent records) lower than a predefined, conservatively high threshold were excluded. More specifically, we defined a month with valid data if at least a fraction q = 0.9 of the admitted patients were in Status 4. To account for possible statistical fluctuations we allowed for 1σ tolerance. That is, in a month with N admitted patients, we required that at least

$$round\left(Nq - \sqrt{Nq(1-q)}\right)$$

patients had complete and consistent records.

In this expression from the fraction q of the N admitted patients (Nq) we subtracted its standard deviation, computed as $\sigma = \sqrt{Nq(1-q)}$.

After passing the validation system, data from ICUs with at least four months of valid data were merged to form the aggregate database, ready for statistical analyses. This tried and tested process served to guarantee the superior quality of the collected data.

Patient follow-up data collection

Follow up was two-tiered for both adult and paediatric patients. All patients (or their parents/guardians/legal representatives in the case of children) consented to be contacted for follow-up assessment

Adult patient follow up

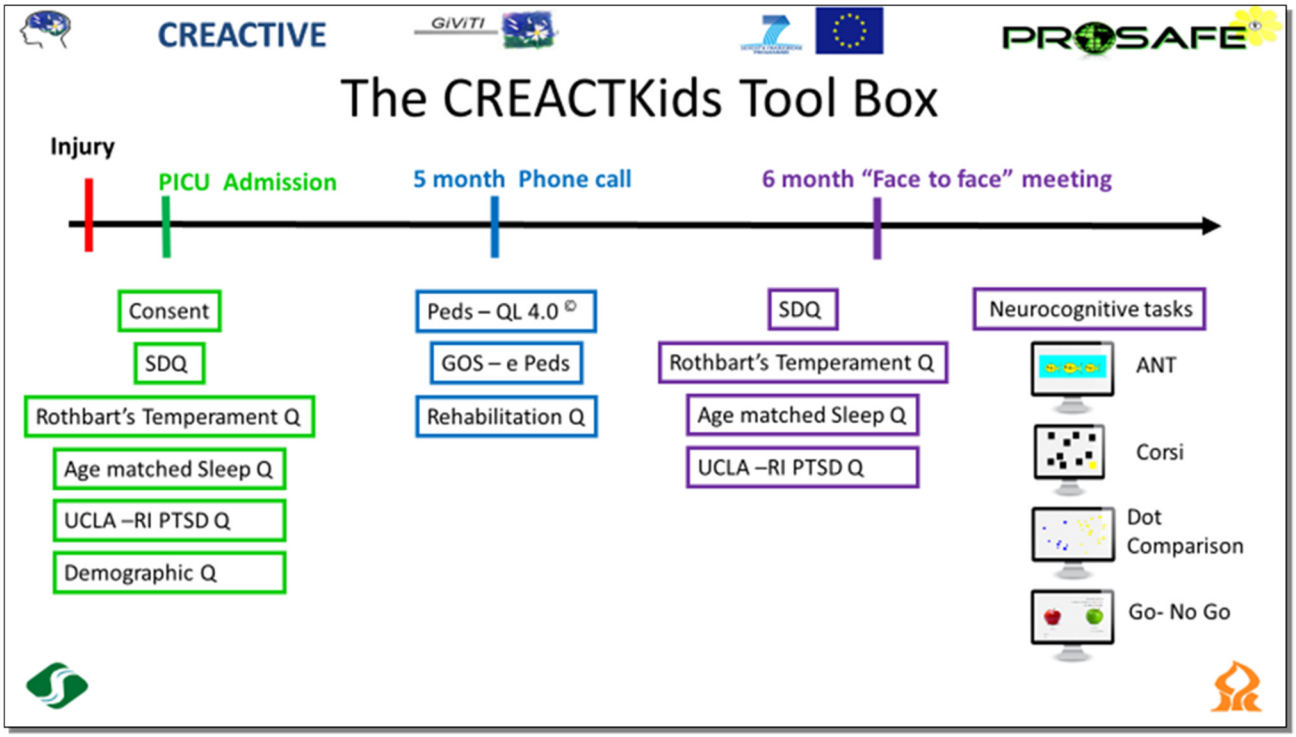
The first level of adult follow up consisted of a semi-structured telephone interview based on administration of the Glasgow Outcome Scale Extended (GOSe) questionnaire to explore outcome (death or various levels of disability), the QOLIBRI (Quality of Life after Brain Injury) Overall Scale to assess quality of life, and an ad hoc Rehabilitation Pathway measure, developed by the CREACTIVE Follow-Up Advisory Board, to objectively determine type and length of rehabilitation received by the patient. Patient telephone follow-up started, in the first Reporting Period, in mid-September 2014 and at **31 March, 2019 had been performed for over 3600 adult patients. Considering that over 2200 patients died before six months, outcome information is available on approximately 5,800 patients.**

The second level consisted of an ambulatory visit carried out in a selected subset of ICUs at 12 months, i.e. six months after the preliminary telephone interview. Patient follow-up was preferably performed by nurses, clinical psychologists or other ICU providers since they were in a position to continue this activity beyond the

duration of the CREACTIVE project. One of the aims and expected impacts of the project was in fact for patient follow up to eventually become part of routine practice at the ICU. The ambulatory follow up was developed by a multidisciplinary Follow-Up Advisory Board formed by clinicians, neurorehabilitation specialists, clinical psychologists, epidemiologists, statisticians, patient advocates, and patients.

CREACTKids follow up

A separate follow-up protocol was developed for children. The neurocognitive follow-up package (referred to as the CREACTKids Toolbox) was built under the leadership of neurocognitive development psychologists from BGU department of Psychology. Tools to evaluate neurocognitive effects post TBI were included with age-matched study packages formed by questionnaires and computer-based tasks. The assessment took place in three stages because it was very time consuming. The first assessment was at ICU admission/ during ICU stay to assess premorbid cognitive status. The second was by telephone at five months after the TBI event; an ambulatory visit was then held at six months after the TBI event.



Data collector training

Each country coordinator was entrusted with training and providing support in CREACTIVE data collection for ICU providers. A senior intensivist at each ICU was responsible for the protocol and data integrity. A detailed online operating manual drawn up by NEGRI was available to all collectors.

Since patient follow up was not part of routine practice in the vast majority of participating centres, a highly structured training programme was implemented to train staff in telephone and ambulatory follow up, including workshops held in Italy.

Data collection monitoring

Besides using the online monitoring system, country coordinators supervised ICUs participating in their national networks through periodic site visits. Since Italy had a large number of ICUs participating in the project, seven monitors were extensively trained to provide support to a certain number of participants, partly based on geographic distribution. Monitoring activities also included teleconferences, e-mail exchanges and telephone support. The "Analyser" built into the CREACTIVE system was regularly used by the Country Coordinators, and in some cases by the project managers, to monitor national ICU compliance and progress.

Continuous data collection

Data was gathered throughout the project but did not cease at the end of the funding period. The consortium will benefit from continuing the collection programme and processing the data. It is stressed that sensitive patient data are accessible only by the admitting ICU. Data used for statistical analyses and reports are completely anonymised.

3.5 Statistical clinical analysis and data reporting

NEGRI was in charge of statistical analysis and leader of Work Package 5. WP5 was devoted to statistical analyses on the collected data, designed to describe the clinical epidemiology of TBI and predict patient outcomes based on the application of multivariate models. Collected data were used to produce personal, national and international reports, providing the participating ICUs with a tool for evaluating own strengths and weaknesses and for comparing own performance with other ICUs at local, national and international level, on which basis to establish best practices. These multivariate models were also the foundation on which to conduct appropriate analyses on the effectiveness of different interventions. Within the framework of the InTBIR data sharing pilot, the team performed data analyses using the HBP/MIP data sharing platform described in WP3 and WP7.

Describe the clinical epidemiology of TBI in the participating countries

A key objective of CREACTIVE was to describe TBI epidemiology, its impact on long-term patient outcomes, and the variability of treatment approaches. Data included in previously existing registries were collected from highly specialised care facilities with vastly different research methods and information formatting. This scenario meant, on the one hand, that data did not reflect the complete picture, considering that a considerable proportion of TBI patients were admitted to non-specialized centres, and on the other, prevented collected data from being meaningfully utilized and analysed. The CREACTIVE Consortium contributed to the InTBIR collaborative effort by collecting data in 7 countries in the specific area of moderate-to-severe TBI and by gathering data not only from highly specialized facilities, which would introduce an important selection bias, but also from adult and paediatric ICUs in small peripheral, regional referral, teaching and non-teaching hospitals, thus covering the whole spectrum of facilities caring for patients with moderate to severe TBI of all ages.

Address the problem of missing data

Missing data potentially undermine research results. To address this problem the statistics team did not apply methods to replace missing information, as multiple imputation, except in very specific cases, as for validation of the CRASH and IMPACT scores, due to the many acknowledged pitfalls. Conversely, it would be wrong to omit only patients with incomplete data from the analyses since this could skew the estimates due to a potential selection bias. Patients with incomplete data may represent a special population subgroup. If these were the only patients to be omitted from the analysed group, the statistics would no longer represent the whole group. To tackle this problem, it was CREACTIVE policy omit from the data of each individual ICU any patients recruited during the months when the validity percentages were below a given threshold (around 90%, depending on the average number of patients admitted, see paragraph 3.4.2).

Provide each ICU with continuous monitoring, descriptive reports and personalised information according to own requirements

Various statistical reports referring to the previous year were generated: Collective (all project data); National (national situation of each participating country); and Individual (situation of each individual participating ICU). These were published twice yearly: one in the summer, describing the clinical data and outcome (up to hospital discharge); and one in the autumn, adding information collected at 6-month telephone follow-up interview. NEGRI was in charge of producing, editing and publishing the reports. During the rest of the year, individual ICUs could request reports providing overall and individual ICU data at any given time.

The statistics team produced a template for the descriptive report. This was used to describe both the overall case series and individual ICU case series. The team also assisted participating centres requiring information for internal controls or for requests from their managing departments.

Monitoring report

Monitoring reports could be either centre- or country-specific. The reports of the individual centres were also made available on the CREACTIVE Analyser and could be produced separately on a yearly basis. The status of each centre in terms of valid data was compared with the status of the ICUs taking part in CREACTIVE collectively. Data validity was analysed both in terms of the validity of the PROSAFE Core data (both patients as a whole and CREACTIVE patients), and the validity of the CREACTIVE data. Lists were provided of patients in Status 1 (with related errors), Status 2 and Status 3. The final section of the monitoring report included an analysis of follow-up status, with the list of patients eligible for follow up.

The country-specific monitoring report followed the same structure as the centre-specific monitoring report. For each validity session it provided the status of all ICUs taking part in CREACTIVE, the status of all ICUs in the country concerned and the status in each centre in the country. The lists of patients were not included.

Validity reports on the Analyser

These were centre-specific reports designed to investigate the validity of the data included in the PROSAFE CRF in general and CREACTIVE CRF in particular, on a monthly (or periodic) basis. The number of patients eligible for CREACTIVE (absolute or percentage values), the complete number of patients (absolute or percentage values), and the number of patients with the follow-up protocol performed (absolute and percentage values) were provided for each month/period. As regards follow-up data, the list of patients to be followed up was provided according to a colour scheme, based on the time elapsed since the trauma event.

Provide each ICU with tools designed to compare own quality of performance in treating TBI patients with average adjusted rates

This approach provided ICUs with appropriate tools for self-evaluation of weaknesses and strengths in own care performance and enabled identification of ICUs of excellence, permitting good exchange of practices and ultimately quality improvement.

Perform comparative effectiveness analysis

Apart from descriptive statistics, which are useful for illustrating general and local clinical epidemiology of TBI in the various participating countries, the core of the analysis was to compare treatments using the comparative effectiveness (CER) approach. Statistical analyses adhered to the guidelines laid down by the US Agency for Healthcare Research and Quality.

The effectiveness of treatments was investigated on different outcomes. Three different outcomes were considered: short-term (hospital) mortality; medium-term (six-month) mortality; and medium-term (six-month and twelve-month) disability. Short-term outcome refers to mortality at the time of discharge from the last admitting hospital following TBI. The underlying rationale was that the patient no longer required aggressive, specialised, interdisciplinary care, making it the first useful time-point at which to assess the effect of clinical intervention in patient outcome from the acute phase of the injury.

The core of the analysis, as for any CER, was to predict outcomes through multivariable models (mainly by logistic regression). The GiViTI Calibration Belt was used both in the development of the models and to assess the performance of each ICU.

The aim of the analysis was to determine the most effective treatments according to patient characteristics and type of injury. The CER analyses performed by the NEGRI team benefited from a well-calibrated prognostic model and were conducted using the propensity score approach, to adjust for different indications to treatments. This was the approach used to analyse patient centralisation. The team built a propensity score yielding the probability, for each patient, of being centralised based on his/her clinical characteristics. The first analytical

approach was to use propensity score matching, involving matching each patient in a hub ICU with a patient in a spoke ICU. Hence, one of the two patients was in a hub and one in a spoke but, according to their characteristics, they had the same probability of being centralised. This provided comparable case mixes (the propensity score is the method commonly used to mimic randomisation in non-randomised studies). Further adjustments in case mix were made also considering the severity of patients, as yielded by the polytomous model (see below). After the funding period the WP5 statistics team will further investigate TBI patient centralisation. Although analysis of this aspect is relatively well advanced, definitive analyses will continue to be performed on the complete case set at the end of the project life. The propensity score will be further enhanced to analyse not just Hub vs Spoke, but also, if feasible, Hub vs Spoke with Neurosurgery vs Spoke without Neurosurgery. The polytomous model may possibly be developed to analyse 4-level rather than 3-level outcomes.

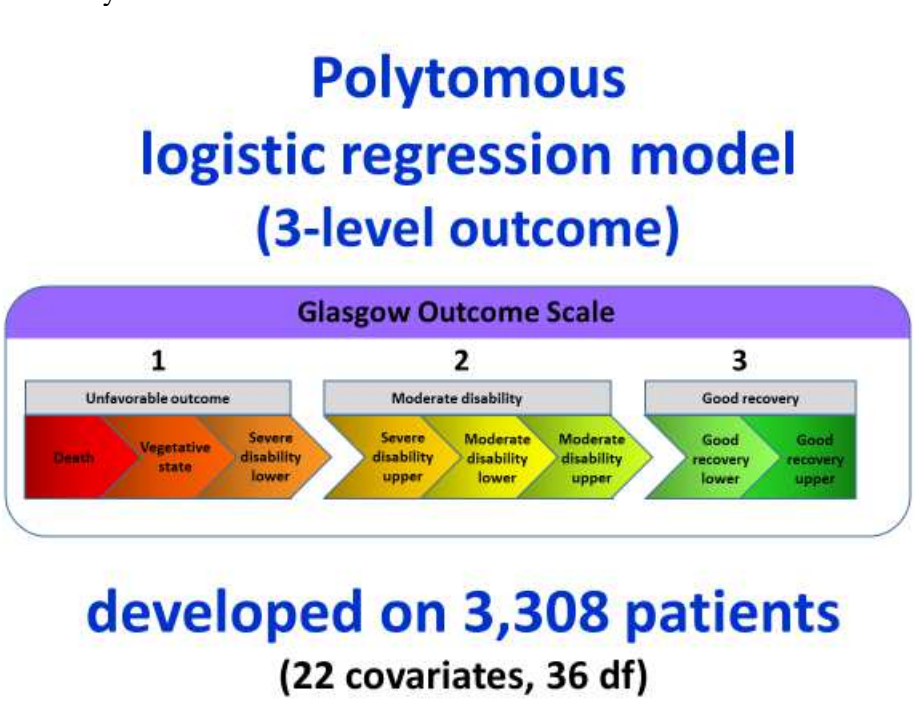
Build a 3-level polytomous prognostic model

The three outcome levels are based on the GOSe at 6 months:

- level 1 – death/vegetative state/severe disability lower level;

- level 2 – severe disability upper level or moderate disability;

- level 3 – good recovery.



The model built by NEGRI is based on input from patients' ICU admission characteristics (both general clinical and TBI-specific) and yields three probabilities for each patient, one for each outcome value. That is, the probability, based on patient characteristics, of a 6-month outcome of death/vegetative state/severe disability lower level severe disability upper level; the probability of a 6-month outcome of severe disability upper level or moderate disability; and the probability of a 6-month outcome of good recovery. The 3 probabilities are complementary and have a combined sum of 1. This model was used to compare expected with observed outcomes of patients with TBI in each ICU, i.e. it was adopted as the basis for comparative effectiveness analysis and to assess how far TBI patient outcomes depend on resources available in the admitting facility.

External validation tests are currently being performed on the polytomous prognostic model using complete pools of data. If the model does not prove valid, it will be rebuilt.

Determine the prognostic significance of phenotypic biomarkers

A monthly report was drawn up to monitor the status of all centres collecting biological material as part of the biobank sub-study (Cyprus, Hungary, Italy and Slovenia). A descriptive report was periodically drawn up on patient data collected in the biobank. At the end of the funding period, over 3600 samples had been collected on over 2000 patients. The CREACTIVE Consortium therefore achieved its original targets.

During the Reporting Periods 2 and 3, a pilot study of blood biomarker candidates was performed by three outside laboratories (Olink Proteomics, Uppsala; MSD, Milan; and Humanitas, Milan), on 80 patients with available biological samples, to assess the association between biomarkers and several subgroups of patients with TBI. 107 biomarkers were assayed. The 80 patients were chosen according to pre-specified inclusion criteria based on the Glasgow Coma Scale score. It was decided to have three equally sized groups that were homogeneous in terms of GCS: 26 patients with GCStotal=3; 27 patients with GCSmotor=5 and GCStotal=7-8; 27 patients with GCSmotor=6 and GCStotal=13-15). A novel cluster analysis was performed on the most promising biomarkers to see how far they were able to predict outcome. Selection of the biomarkers to form the clusters was based on the *p* values yielded by the biomarker analysis. The analysis was performed using the polytomous logistic regression model illustrated above. An in-house expert in cluster analysis was involved to optimize the data analysis.

The identification in the pilot study of 29 promising biomarkers for TBI prognosis prompted replication of the study in a larger, more representative number of patients, considering that confirmation of the pilot results could mark an important advance in prognosis in the very acute phase of the injury, helping physicians to make more accurate clinical decisions at that stage. The Consortium opted to have as large a sample as possible (2000 samples), collected towards the end of the project. Consequently, only part of the statistical analyses could be performed during the CREACTIVE funding period. The analyses will nonetheless continue with other sources of funding, as part of the CREACTIVE legacy. The following are some preliminary results.

In the analyses performed on the 80-patient pilot, with samples drawn at ICU admission, 23 biomarkers (assayed by Olink Proteomics, Uppsala) associated with TBI were identified. The analyses on 2000 samples confirmed 17 (74%) of these 23.

It was not possible to compare results on samples drawn at 5 days after admission with previous findings since the pilot study did not include samples drawn at 5 days. What did emerge is that at admission, 75 biomarkers were associated with trauma (of which 21 were associated only with cranial and 54 with both cranial and extracranial variables), while at day 5, 70 biomarkers were associated with trauma (of which 28 were associated only with cranial and 42 with both cranial and extracranial variables). Hence at day 5 more variables were associated solely with cranial variables, suggesting that inflammation linked with extracranial trauma could resolve earlier than 5 days and thus show more rapid dynamics. This was our hypothesis.

Evaluate the association between TBI patient outcomes and available resources at admitting ICU

Work started to assess the extent to which TBI patient outcomes depend on resources available in the admitting facility. This will be investigated in greater depth in the future. The models developed for the purpose take into account the resources available in the individual ICU (e.g. doctor to patient ratio; bed occupancy rate; GDP parity purchase power) together with patients' clinical characteristics at ICU admission (e.g. comorbidities, Glasgow Coma Scale score, organ failures, physiological derangement) thus greatly limiting context-sensitive variable bias. The aim was to generate a model that calibrated well, overall and in each subset identified by the variables included in the model (e.g. septic shock, surgical status, gender).

Identify centres of excellence in treating TBI patients, fostering exchange of good practices and quality improvement

Analysis based on the GiViTI Calibration Belt provided detailed information on ICU performance and allowed identification of centres with the best performance in TBI treatment and those with poor results at any one time.

The analysis also allowed to identify features (e.g. ICU or hospital organization, existence of high levels of specific skills) that determine the high quality results of the best centres. The aim of this was to promote collaboration between high-performing ICUs and those needing to improve their skills in TBI treatment. This was also obtained through targeted educational campaigns and by organizing fellowships to exchange best practices among ICU staff. The effect of implementation of corrective interventions in low-performing centres was monitored using the same methodology.

Evaluate the impact of sociodemographic variables on outcome

CREACTIVE exploited its large database to analyse the role of age, gender and other demographics in TBI patient management, addressing their impact on head injury type, treatment and rehabilitation options available across the continuum of care. Rates of change in clinical, functional, behavioural and neurocognitive outcomes, as measured at telephone and face-to-face follow-up, have been evaluated.

Preliminary analyses yielded an adult M/F admissions ratio of 1:2.8, and a lower adult mortality rate in males than in females (29.3% vs 32.4%). In addition, findings suggest less probability of an unfavourable outcome in patients with a higher educational level.

Perform data analyses using the HBP/MIP data sharing platform within the framework of the InTBIR data sharing pilot

CREACTIVE and HBP/MIP jointly undertook to develop a web-based platform on which to run analyses and algorithms on combined data. Development of a pilot architecture started in July 2016 to map and configure the common data elements on TBI and to retrieve over 1,000 admissions from real CREACTIVE data. A common series of metadata agreed on with the team from CENTER TBI will subsequently be incorporated as the first step towards permitting joint data analyses, validating the Core IMPACT score as the starting analysis and subsequently the CRASH score, which together constitute the scores most commonly used in TBI.

Other WP5 activities:

Functions to assess the calibration of logistic regression models with the GiViTI Calibration Belt

The tools developed to permit ICUs to assess their own performance compared to the national ICUs collectively (standard mortality ratio [SMR], Variable Life Adjustment Display [VLAD], calibration belt) have been made available to the entire scientific community thanks to the development of a special R package which is downloadable free of charge at: (https://cran.r-project.org/web/packages/givitiR/index.html), and a dedicated command in Stata software.

A distributed version of the Calibration Belt and Test was developed by generalizing the algorithms included in the GiViTI R package to a federation of databases. The HBP group was provided with this code for implementation in the MIP platform.

CREACTIVE tutor training

The statistics team assisted the Coordinating Centre by periodically providing training and updating sessions for CREACTIVE tutors on the available performance assessment tools. These included training and updating sessions on use of the PROSAFE and CREACTIVE software, held at the annual Italian National CREACTIVE meetings each autumn.

Assistance with PhD theses

The WP5 statistics team provided support for exploratory analyses performed on CREACTIVE data to establish any sociodemographic differences in TBI: in terms of physiology, care, outcome, rehabilitation. This will form the basis of a PhD thesis by a student from Nicosia University.

Assistance with CREACTIVE dissemination activities.

Assistance was provided in drawing up the Consortium's platform and poster presentations**.**

3.6 Biobank and analysis of phenotypic biomarkers and clinical imaging

Establish a CREACTIVE repository within the Coordinator's existing biobank

WP6, led by NEGRI, involved the implementation of a centralised biological repository within the existing biobank based at the Coordinator's premises. It served as a bank for plasma, serum and cerebrospinal fluid (CSF) samples to test for phenotypic biomarkers of TBI that could influence disease progression and outcomes and consequently impact on the effectiveness of treatment. A second repository was implemented to collect patient imaging data. Tests performed on this material provided additional clues to the role of biomarkers in TBI progression and response to treatment.

Patient samples collected in the CREACTIVE repository, from a subset of ICUs, were handled and stored following a quality assurance system (certification ISO 9001:2015), envisaging all standard operating procedures for biobank management: training of qualified personnel; control of facilities and equipment (mainly ultralow temperature freezers); collection, transportation and storage of biological samples; distribution of biological samples; management of informed consent; technical and scientific committee; logical and physical data security; contingency plan; disaster plan.

Specific biological repositories were established within the existing biobanks at KCLJ, MHEK and Nicosia for collection of samples in Slovenia, Hungary and Cyprus. A simple, uniform, efficient logistics protocol was also drawn up for the safe shipment of biological samples on dry ice using a hub and spoke approach.

Biological substudy procedures

Biological samples were collected for phenotypic biomarker analysis. Blood samples were obtained as part of the samples routinely drawn to guide clinical treatment at ICU admission and at 4-5 days after trauma. An additional withdrawal was made during the outpatient visit 12 months later, in centres taking part in this substudy.

CSF was collected only in patients undergoing external ventricular drainage as part of routine clinical treatment. In such cases, a CSF sample was taken 2-6 after hours after inserting the device and 4-5 days after the trauma. The biological samples were identified by an anonymous code, to prevent patient identification, and shipped to the consortium's central laboratory at Mario Negri Institute in Milan.

Accrual of samples stored in the CREACTIVE biobank

Twenty-five CREACTIVE centres, based in Cyprus, Hungary, Italy and Slovenia, participated in the circulating biomarker substudy. The protocol for biological sample collection was approved by the competent ethics committee at all centres. Copies of the related documentation were collected by the biobank. Disposable materials (a total of 3615 individual kits valid for one patient and one clinical visit) and detailed instructions for the biological samples to be collected were distributed to the centres. The first sample was stored in the biobank on 1 February, 2015. At 31 March, 2019, blood samples had been collected for a total of almost 2200.

A protocol for access to stored material beyond the life of the project was drawn up as a project deliverable. The repository of biological samples on over 2000 patients, and the imaging data repository on almost 1300 patients will be made available to the scientific community for research use, with access being granted through the appropriate channels.

Assays

Different molecules (biomarkers) were assayed in plasma and serum samples collected at different time points. The preliminary list of the molecules assayed was as follows: neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), glial fibrillary acidic protein (GFAP), Tau protein, ubiquitin C-terminal hydrolase-L1 (UCH-L1), brain derived neutrophic factor (BDNF), Interleukin-6 (IL-6), Olink Inflammation panel (a panel of 92 inflammation-related protein biomarkers) (Olink Proteomics, http://www.olink.com/), pentraxin-

3 (PTX3), a marker of innate immunity and vascular damage, interleukin-1 receptor antagonist (IL-1ra), and soluble interleukin-1 receptor type II (sIL.1RII).

Preliminary results of the pilot assessments performed on the first 80 plasma samples were presented:

- at the CREACTIVE Symposium, "*CREACTIVE and BIO-AX-TBI: Integrating circulating and neuroimaging biomarkers to improve phenotyping in TBI*," held at the 4th Federal Interagency Conference on TBI in Washington DC on 13 June, 2018;

- as an oral contribution, "*Circulating biomarkers for TBI prognostication. First results from CREACTIVE*," at the 2nd Frontiers in Traumatic Brain Injury Conference in London on 5 July, 2018;

- as an oral contribution, "*Circulating biomarkers for TBI prognosis*," at 7th International Initiative for Traumatic Brain Injury Research (InTBIR) Conference; and

- at the final CREACTIVE Symposium, "*Can we improve prognostication in TBI? Preliminary results from CREACTIVE,",* held in Brussels on 21 March, 2019 as part of ISICEM 2019.

The CREACTIVE Consortium has been approached by the National Enterprise for NanoScience and Nanotechnology (NEST) Laboratory - Istituto Nanoscienze, CNR and Scuola Normale Superiore di Pisa, Italy. The NEST team has proposed to test a technique to assess 4-8 biomarkers at the bedside in the space of one hour. The extensive biomarker assays performed by the CREACTIVE Consortium on 2000 patients may provide some very interesting information on which biomarkers could be selected for this technique.

Collect TBI imaging data

The imaging biobank was developed by Orobix and deployed on infrastructure provided by NEGRI. A user-side application was developed for retrieval, review, annotation, deidentification/anonymisation and collection of medical imaging data. The application securely connected to the imaging biobank.

Among the challenges posed by the imaging substudy was the absence of a common CT and MRI imaging protocol and current best practices in clinical imaging of TBI patients. This choice was made to avoid interference with radiological practice at centres and to maximize the amount of data obtained for the study, at the expense of a greater burden during the analysis phase. Accordingly, extensive calibration and validation of the image analysis pipeline was required to ensure performance for all centres.

Briefly, all CT scans collected in the first 10 days of admission of patients with TBI were annotated by a clinician to roughly locate the primary focal, haemorrhagic lesion(s), anonymized, and then uploaded to a centralized imaging biobank for further processing and quantification at the central level. The module was designed to automatically remove sensitive information from the DICOM header (face features such as eyes, nose and mouth).

Collection of imaging data officially started in March 2015. Up to the last reporting period, **a total of 4693 series had been collected from 1260 patients.** Series were quality controlled for the presence of strong artefacts (due to the intracranial, radio-opaque devices in the scan), which resulted in a **total of 3846 quality-controlled series from 1096 unique patients.** The dataset was employed to develop a deep-learning model for the automated segmentation of intraparenchymal haemorrhages and oedema, allowing prospective users to identify lesions from CT scans and track them over time for research purposes. The machine-learning methodology required a curated training set of CT scans in which both haemorrhages and oedema were outlined. To this end, in the last reporting period a team of expert operators (neuroradiologists and medical researchers) performed manual segmentation on a subset of the data set. Specifically, a total of 1158 series were manually segmented, making the CREACTIVE imaging biobank a **unique** dataset for training and validation of machine-learning methods on TBI from CT imaging.

The dataset was employed to train a deep learning-based, dense segmentation method (U-Net) for automatic segmentation and sizing of lesion and oedema. A detailed technical report describing the work in progress was drawn up.

Clinical data for 394 out of 567 patients with an annotated lesion were extracted to the main dataset, for a total of 1204 series. Of these, 64 patients had recovered, 92 survived with disability and 238 deceased. This dataset was employed to research into the use of raw imaging data in addition to clinical data as an input to a neural network model to predict outcome. Through its convolutional layers, the model is trained to recognize image-based patterns that characterize the lesions and their relation with outcome. The performance of the final model will subsequently be compared to the model developed by partner NEGRI on clinical data, to evaluate the potential for augmenting epidemiological models with imaging data.

Preliminary results of the imaging analyses were delivered with the following platform presentations:

- *CREACTIVE and BIO-AX-TBI: Integrating circulating and neuroimaging biomarkers to improve phenotyping in TBI,* as part of the CREACTIVE symposium at 4th Federal Interagency Conference on Traumatic Brain Injury, Washington, 11-13 June, 2018

- *Using CT scans in TBI: deep-learning techniques,* at the Italian National CREACTIVE meeting, Abano Terme, Padova, 7-9/11/2018

- *Imaging biomarkers in TBI: machine learning applied to TBI imaging,* as part of the CREACTIVE final symposium *Can we improve prognostication in TBI? Preliminary results from CREACTIVE* held at ISICEM 2019, in Brussels on 21 March, 2019.

- *Deep learning as an automatic image analysis tool* delivered by Orobix at the final meeting of the Italian National CREACTIVE network on 25 March, 2019.

The final segmentation model for haemorrhagic lesions and oedema from CT imaging will be published and made available to the participating centres through a clinical pilot. Its performance and potential impact on clinical decision-making will be assessed through the pilot study protocol.

Partnerships are in the meantime underway with Imperial College London, formally through the BIO-AX-TBI (ERA NEURON NET) project, and Cyprus University Nicosia to exploit the clinical and imaging data collected in the CREACTIVE registry.

4. Impact of the CREACTIVE project

The results obtained during the CREACTIVE project have had several important scientific, medical and socioeconomic impacts. The project will continue to produce important scientific information in the coming years from the ongoing analyses on clinical data, biological samples and clinical imaging data.

4.1 Impact on the scientific community

The CREACTIVE project has gathered data on almost 8000 moderate to severe TBI patients (without any selection), and from all types of critical care facilities (not restricted to tertiary ICUs). Such full coverage will help ensure **better classification of TBI**. Various types of data have been collected to extend the analysis (clinical characteristics, clinical imaging, phenotypic biomarkers, healthcare resource availability, process of care adopted) and to **explain different types of outcome** (short- and long-term mortality, and disability). These high quality, highly representative TBI data will be readily **available for secondary analysis** by the scientific community.

The consortium has developed innovative statistical tools, including a **prognostic model** designed to **assess the effectiveness of clinical interventions** and to **identify excellence and best practice**. It is based on input from patients' ICU admission characteristics (both general clinical and TBI-specific) and yields three probabilities for each patient, one for each outcome value (the probability of a 6-month outcome of death/ vegetative state/severe disability lower level severe disability upper level; of a 6-month outcome of severe disability upper level or moderate disability; and of a 6-month outcome of good recovery). It is used to compare expected with observed outcomes of TBI patients in each ICU, i.e. it can be used as the **basis for comparative effectiveness analysis** and to **evaluate the extent to which TBI patient outcomes depend on the resources available in the admitting facility** (e.g. doctor to patient ratio; bed occupancy rate; GDP parity purchase power) **and patient conditions** (e.g. comorbidities, Glasgow Coma Scale, organ failures, physiological derangement), thus greatly limiting the context-sensitive variable bias. The model calibrates well, overall and in each subset identified by the variables included in the model (e.g. intraparenchymal haematoma, surgical status, gender). This was obtained using another statistical tool created ad hoc: the GiViTI calibration belt. The CREACTIVE prognostic model **fills an important gap** in the field of TBI where such tools were lacking or calibrated poorly when applied to an external cohort.

In the framework of the International Initiative for Traumatic Brain Injury Research (InTBIR) the CREACTIVE Consortium has established a **collaboration with the Human Brain Project/Medical Informatics Platform (HBP/MIP)** to develop and pilot a federated, web-based **data-sharing platform** on which to run analyses and algorithms on combined data for simple statistics purposes. The aim is to share the platform first with other European projects participating in InTBIR (CENTER-TBI) and subsequently with other InTBIR consortia from North America. Efforts have been made to participate in activities to exchange information and data organized by other InTBIR projects in Europe, USA and Canada, with a view to improving knowledge of TBI and harmonising research efforts. These include the INCF Workshop, *Towards alignment of brain initiatives in support of clinical data,* held in Stockholm in April 2018 and the DAQORD (Data acquisition, quality & curation for observational research design) working group meeting and Consensus Conference in Washington, in September, 2018, whose results will be transferred to the scientific community.

CREACTIVE Consortium members have **presented preliminary findings** of the project to the scientific community **at key annual congresses and other specialty meetings** in Europe, North America and Asia. These include ISICEM, ESICM, the American Congress of Rehabilitation Medicine, InTBIR meetings, the Conference on Paediatric Acquired Brain Injury, European Society of Paediatric Neonatal Intensive Care, Frontiers in Traumatic Brain Injury, and more. Additional details can be found in the Dissemination Tables below.

The CREACTIVE legacy

The registry housing 60 months' collection of high quality, validated clinical data on almost 8000 patients, the biological repository of biological samples on over 2000, and the imaging data repository on almost 1300

patients will be made available to the scientific community for research purposes, with access being granted through the appropriate channels. Partnerships are in the meantime underway with Imperial College London, formally through the BIO-AX-TBI (ERA NEURON NET) project, and Cyprus University Nicosia to exploit the clinical and imaging data collected in the CREACTIVE registry.

The collaboration with HBP/MIP will continue through an Infrastructure Voucher programme promoted by HBP, giving free access to HBP/MIP services and engineering/development support for a further 12 months. The remaining work to set up the data sharing platform will be completed under the Voucher programme (which will run until 31 March, 2020). The platform will constitute an important legacy of CREACTIVE, permitting the huge harmonised datasets collected under the InTBIR umbrella to be exploited more extensively, providing a greater return on investment for funders, and enabling deeper understanding and insights than individuals in each centre could obtain singly.

4.2 Impact on patients and their families

Participation itself in clinical research projects has been associated with an increase in the quality of care provided. This is due to a number of different factors, including increased attention to enrolled patients, adoption of more standardised protocols, enhanced knowledge on the subject matter among attending physicians, more incisive exchange with colleagues, and the transfer of clearer information to patients and their relatives.

Patients have directly benefited from the 6- and, for some, 12-month follow-up visit, where neurological and psychological sequelae of TBI, as post-traumatic stress disorder, cognitive impairment and disturbed sleep, have been systematically evaluated. For many patients, this has been the opportunity to have their situation reviewed by health personnel, with admission in some cases to specific rehabilitation or social reintegration programmes. In general, following up patients has helped build awareness about long-term sequelae of TBI.

By developing and applying Comparative Effectiveness Research (CER) for TBI, with a view to identifying the most appropriate interventions and determinants of best practices in the intensive care setting, TBI patients are gaining from the resulting improvements in quality of care. The analyses have been designed to identify not only the most effective single or more complex bundle of interventions within ICUs (e.g. patient centralisation, intracranial pressure (ICP) monitoring, decompressive craniectomy), but also the best TBI care pathway. Since patients have been followed up at 6 and, in a subset, at 12 months, it is possible to reconstruct the care pathway of each one and establish the extent to which disparities in access to post-acute care influence the recovery process. This is clearly of advantage to the patient.

Account has also been taken of issues related to cognition (thinking, memory, and reasoning) and behaviour or mental health in general (depression, anxiety, personality changes, aggression, acting out, and social inappropriateness), which are among the most frequent sequelae of TBI. The follow up protocols implemented in this project have taken these factors into account and this, too, has benefited patients.

Children were given specific consideration in the CREACTIVE project, forming the special subproject, CREACTKids. They were differentiated both at the level of the case report form (eCRF), which was separate from the adult CRF, and in terms of post-TBI outcome measures, which are difficult to assess in this age group. Most functional and cognitive tools used to evaluate outcome post TBI need patient cooperation, which can pose problems in children and rely mainly on third party information (from parents, caregivers, teachers, etc.). The quality of the data of tools available prior to the CREACTIVE project varied among age groups and studies, questioning their validity. The development by the BGU team of the objective, quantitative and holistic CREACTKids Toolbox, has proven very useful.

Tangibly, patients and their families have been reached via specific information leaflets about the project, tailored publications in popular science journals, as Brain Injury Professional, and through the website.

The CREACTIVE legacy

The CREACTKids Toolbox, outlined above, is an example of exploitable foreground that will continue to be of advantage patients and their families going forward. It will continue to be used to follow-up paediatric patients as this practice eventually becomes part of routine care and in the proposed 5-year follow-up protocol. The versatility of the CREACTKids Toolbox means that it can potentially be tailored for the follow up of other pathologies besides TBI.

4.3 Impact on healthcare providers

The first task of the CREACTIVE project was to involve the maximum number of ICUs in each participating country and to extend the data collection to as many facilities as possible, partly with a view to making data collection in each country as representative as possible.

The CREACTIVE project produced personal, national and international reports on performance. ICU providers have directly benefited from receiving their own data in a structured, meaningful form, enabling them to analyse their own results and compare their performance with that of other facilities. These reports have been designed to identify areas of both strength and weakness.

Fellowships, which were part and parcel of the CREACTIVE project, enabled ICU staff (physicians, nurses) and other team members to take part in exchange visits to other units with a view to sharing best practices. This is the ideal setting for singling out weaknesses and drawing up improvement strategies; it is also a particularly useful method of reducing disparities in quality of care among different centres.

Integrating the results of the CREACTIVE project into the wider InTBIR network has contributed to the spread of best practices in the management of TBI patients. The follow-up assessment implemented in the project at 6 and 12 months after the traumatic event was not part of routine practice in the vast majority of centres prior to conduction of the project. Participating healthcare providers were **provided with specific training, including residential training, and updating** from other healthcare providers with extensive experience in trauma patient follow up, in a train-the-trainer, best-practice-sharing setting. Training was also provided in the form of **periodic workshops for personnel** participating in CREACTIVE. Where possible, the follow-up was managed by ICU nurses, for two main reasons. First, since nurses were involved in the treatment of the patients during their ICU stay, they were already familiar with the patients and the acute care delivered, in turn facilitating data collection. Second, they were, and remain, in a position to guarantee continuation of patient follow up beyond the duration of the CREACTIVE project. This will indeed be pursued in many participating ICUs. Education will continue to be provided through **trainer training**.

In addition to obtaining information on patients in the post-acute phase and providing medium-term outcome data on mortality and disabilities, performing patient follow-up has had an important impact on the personnel involved. Following up patients over a longer period than usual enabled providers to assess the evolution of disability over time, patient recovery, and any coping strategies adopted by patients and their families. It also served as a source of information on patients' experiences of the critical care setting. The overall result has been a wider picture of patient care, of which ICU staff are a part, giving more meaning, direction and added value to the acute care pathway and enhancing engagement in the workplace. This finding emerged across all the participating countries suggesting the cross-cultural nature of said experience.

External dissemination activities to reach other health providers also included presentations of the project at pertinent scientific events to build awareness about CREACTIVE and the wider InTBIR Initiative, and of clinical data at speciality conferences and symposia to share the preliminary findings of the project.

The CREACTIVE legacy

Thanks to the project, medium-term follow-up is now becoming part of standard practice, impacting the quality of life of both health providers and patients.

Since the scenario emerging at 6 and 12 months is not the complete picture, the CREACTIVE Consortium has proposed to start 5-year follow up of patients in order to gain better understanding of longer-term outcomes of patients with moderate-severe TBI. Interviewing patients after 5 years will provide a clearer picture of the impact the TBI event has had on them and their families in terms not only of survival but also of long-term disability. The first patients were eligible for five-year follow up from March 2019 (data collection started in March 2014).

4.4 Impact on health and welfare policy makers

The CREACTIVE project has provided evidence-based results on best practices, epidemiology, clinical interventions, and outcomes in TBI patients. To be useful to healthcare and welfare policy makers, these data must be analysed at various levels in order to select information appropriate to purpose.

Data collection under the CREACTIVE project was designed for targeted analysis. Reports present the local, regional, national and international picture and have been tailored according to clinician and policy-maker perspectives. For example, reports are drawn up to provide information for policy makers, at the local level, on proportionality of available resources compared to case-mix requirements; at the regional level, on the lack of centralization of more complex patients into referral centres; and at the national level, on disparities in access to acute and post-acute (rehabilitation) care across regions and according to sociodemographic factors, as age and gender.

The CREACTIVE project sought to transfer these data to the policy makers concerned and to discuss the implications. Dedicated meetings have been organized with these stakeholders at various levels and in the various participating countries, to present the data produced by the CREACTIVE project and the wider InTBIR network.

CREACTIVE legacy

In Italy, several regions, including Tuscany and Piedmont, have agreed to use or are negotiating implementation of the PROSAFE system and with it the CREACTIVE petal for TBI as the regional standard for quality of care in the ICU and of outcome assessment. Local Health Authorities including Treviso and Bologna, again in Italy, are using the CREACTIVE eCRF as their trauma register. The register is currently being extended to include other trauma sites. In Slovenia and Israel negotiations in this direction are underway to discuss implementing the PROSAFE quality of care assessment system as the national standard for care and outcome assessment.

4.5 Impact on the pharmaceutical and biomedical industry

No drug has yet been approved to specifically treat patients with TBI. Developing such drugs is difficult due to the complexity of the phenomena implicated in the different phases of the syndrome. As is common in all acute conditions, the greatest opportunity for intervention lies in the early phases. Apart from the initial damage caused by the insult, which is a direct consequence of the impact to the brain parenchyma, a key role in the final outcome is played by secondary injury, occurring in the hours and days immediately after the trauma, and resulting from a complex set of cellular processes and biochemical cascades.

The CREACTIVE Consortium is in a position to provide important data to address pharmacological R&D in the field of TBI. Firstly, it has gathered data on almost 8,000 patients, which are representative of the whole panorama. Secondly, as data and sample collection were concentrated in the ICU setting, the onus is on investigation of the secondary phase of injury. Multidimensional analysis has enabled the study of the mutual dependency between different interventions and factors (type and degree of injury, adverse events, quality of care) and final outcome. This is the only way to generate sensible hypotheses on the efficacy of clinical interventions in complex situations, which can subsequently be tested in randomized clinical trials.

Once the final analyses on 2000 biological samples have been completed, the pharmaceutical and biomedical industries will benefit from the development and validation of a pathological and biomarker-based patient

classification system (surrogate markers of injury and recovery outcomes), facilitating the design of well-focused clinical trials for new medications/devices/consumables.

CREACTIVE has entered into collaborations with Olink Proteomics, Uppsala; Quanterix Inc., Lexington; San Raffaele Hospital, Milan; Roche Diagnostics International Ltd, Switzerland; Humanitas Research Hospital, Milan and MSD Milan, in relation to analysis of the biological samples collected in the CREACTIVE biobank and the search for and analysis of biomarkers and biomarker clusters.

CREACTIVE legacy

The CREACTIVE Consortium has been approached by the National Enterprise for NanoScience and Nanotechnology (NEST) Laboratory - Istituto Nanoscienze, CNR and Scuola Normale Superiore di Pisa, Italy. The NEST team has proposed to test a technique to assess 4-8 biomarkers at the bedside in the space of one hour. The extensive biomarker assays performed by the CREACTIVE Consortium on 2000 samples may provide some very interesting information on which biomarkers could be selected for this technique.

4.6 Communication and dissemination activities of CREACTIVE

In this subchapter of Section 4, we outline the contribution of Work Package 7 *Dissemination, communications and networking activities*.

The aim of CREACTIVE dissemination and exploitation activities was to tailor communication, dissemination and networking activities to the various identified target groups in order to convey appropriate information to key stakeholders in the most relevant form with a view to achieving the desired impact. Over the course of the project the Consortium has forged important networking links with other international groups operating in the field of TBI with a view to playing an active part in the wider networking framework and ensuring the sustainability of the CREACTIVE project after the funding period.

The following **key stakeholders** were targeted by dissemination activities:

- Scientific community
- TBI patients and their families
- Healthcare providers
- Health and welfare policy makers
- Pharmaceutical and biomedical industry

CREACTIVE Logo

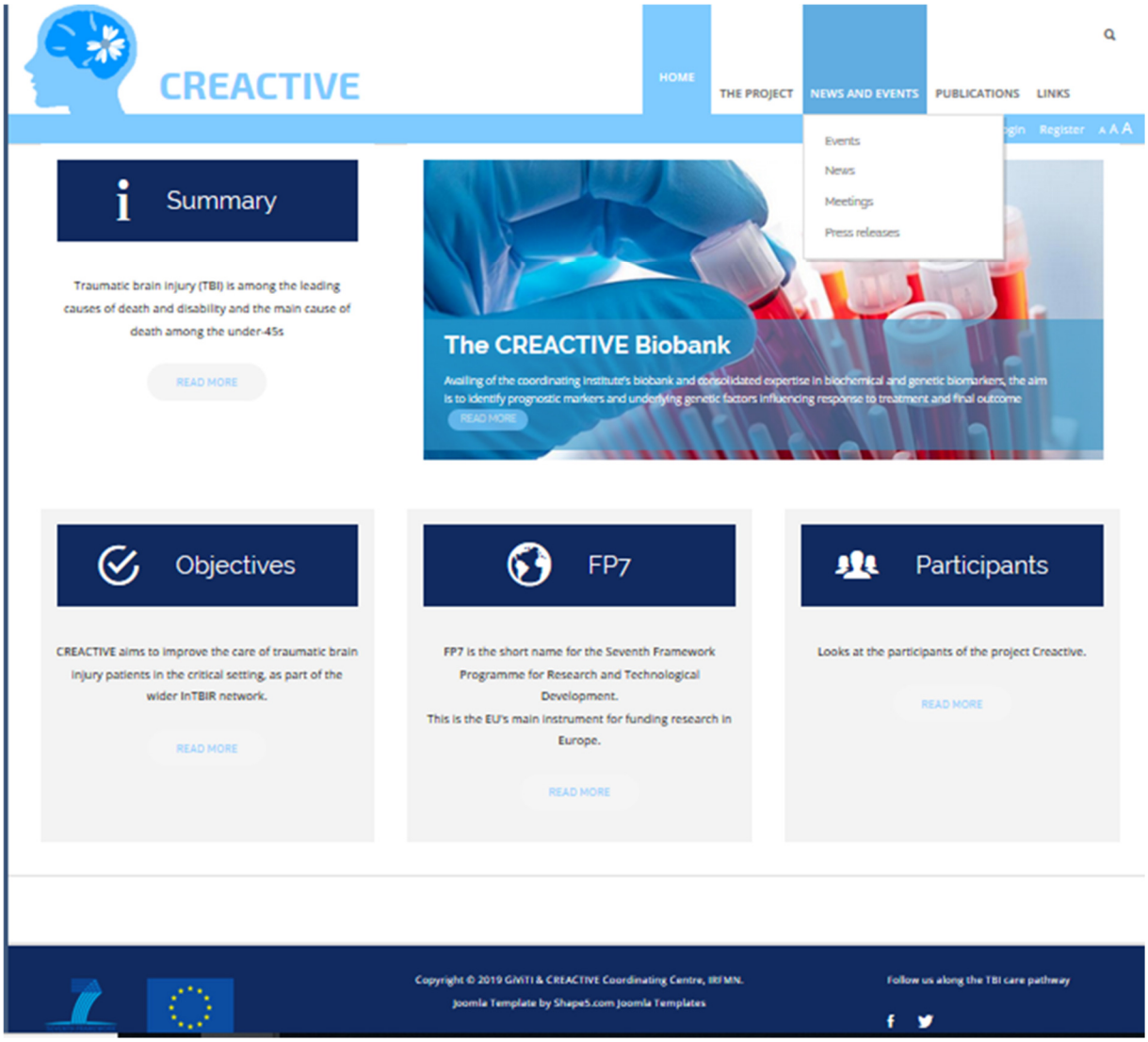
Below is the CREACTIVE logo which appears on all dissemination material, accompanied by a declaration that the project is funded by the European Commission and a disclaimer excluding Commission responsibility for the content of the dissemination material.

The logo was selected by means of a competition held at the start of the project. The winner was announced at the CREACTIVE Kick Off meeting.

The CREACTIVE website

A dedicated project website was created to give visibility to the project and facilitate internal communications among the CREACTIVE partners. It can be accessed online at:

www. http://creactive.marionegri.it/



Presentations at medical and scientific events

During the life of the project, the CREACTIVE Consortium laid considerable emphasis on presentation of preliminary project data at medical and scientific events targeting the stakeholders indicated above. The full list of presentations can be found in the Dissemination tables at the end of this document.

Satellite symposia

Four satellite symposia were organized during the course of the project: one in Italy, two in Washington and one in Brussels.

The First symposium was held in Pesaro in October 2016 during the Italian national GiViTI network meeting to present ongoing project results to the wider ICU community. Approximately 300 delegates took part at the meeting and an interpreting service was provided from Italian to English to Italian.

Contributions were made by Principal Investigators and Project Managers from SBNM, KCLJ, Nicosia, PEPAGNH and Semmelweis, with the support of the NEGRI statistics, IT and management team.

Platform presentations were also given on the subject of Virtual Reality for intensive care medicine, which may have potentially promising applications in the field of TBI assessment and rehabilitation. Narrative medicine and promotion of the caregiver role are likewise very pertinent to the CREACTIVE project in terms of severe TBI patient follow up and rehabilitation.

Two CREACTIVE Symposia, to present ongoing project results to the wider traumatic brain injury community, were organized as part of the 4th Federal Interagency Conference on Traumatic Brain Injury, held in Washington, USA, on 11-13 June, 2018.

The symposia were entitled: *Preliminary findings from the CREACTIVE study on acute TBI in intensive care medicine in Europe,* and *CREACTIVE and BIO-AX-TBI: Integrating circulating and neuroimaging biomarkers to improve phenotyping in TBI.*

The speakers included principal investigators of the study and members of the CREACTIVE multidisciplinary Follow-Up Advisory Board (Prof. Fofi Constantinidou and Dr. Andrea Montis). Both rehabilitation specialists worked in close collaboration with the team throughout the CREACTIVE study and will collaborate with the consortium in future projects to ensure maximum exploitation of the collected data and the sustainability of the project.

The two symposia were planned to coincide with the original end of the CREACTIVE project (30 September, 2018). Following Amendment nr. 3 to extend the project duration by 6 months to 31 March, 2019, it was agreed to organize another, this time final, symposium in Brussels, to disseminate the salient findings to a European audience, thus complementing the mainly North American audiences attending the symposia in Washington.

The final symposium was thus held on 21 March, 2019 during the 39th International Symposium on Intensive Care and Emergency Medicine (ISICEM) attended by over 6000 delegates. Once again, the Discussants were selected to reflect the continuity and sustainability of the CREACTIVE project. Prof. David K. Menon collaborated and will continue in the future to work with the consortium through Center-TBI and the wider InTBIR Initiative. Prof. David J. Sharp is currently coordinating the BIO-AX-TBI project which is nested in the CREACTIVE study and, partly for validation purposes, exploits the extensive, high quality database.

Dissemination in scientific journals

In addition to the papers listed in the tables below, the following papers are currently in the pipeline:

1) CREACTIVE biomarker pilot, describing the methodology applied to the analysis. This is led by KCLJ.

2) A descriptive paper on CREACTIVE is currently being drawn up by MHEK and PEPAGNH.

3) A descriptive paper on the CREACTKids substudy is being produced by BGU.

4) A paper on patient centralization is being written by NEGRI.

5) A manuscript on imaging segmentation is in the OROBIX pipeline.

6) Nicosia is finalizing a paper on 6-month follow up

7) MWU is preparing a manuscript on comorbidities and frailty

8) Another paper on age-related and other demographic characteristics is being compiled by NEGRI.

9) The validation of currently used scoring systems for TBI patients will be the focus of a paper being prepared by NEGRI

Collaboration with other efforts

International Initiative for Traumatic Brain Injury Research (InTBIR)

CREACTIVE has taken an active lead in InTBIR, initially participating in the Data Management, Data Sharing and Clinical Endpoints work group. Following the invited oral presentation, "*Safe Common Clinical Data Sharing*," by the Coordinator, Guido Bertolini, at the 4th InTBIR meeting in Brussels in October 2015, NEGRI was asked to take the lead in promoting data sharing with the InTBIR Consortium. The first step was to form the "Data Sharing" sub-working group, within the Data Management, Data Sharing and Clinical Endpoints work group. After subsequent redistribution of roles, NEGRI was tasked with the co-chair of the InTBIR Policies work group and played a key role in the development of three InTBIR policy documents (Informed Consent guideline, Publication Policy and Data Sharing Principles). NEGRI were also involved in the Biomarker and Data Analytic Work Groups, while Orobix participated in the Neuroimaging Work Group.

Human Brain Project

As part of its data sharing mandate from InTBIR, NEGRI forged ties with the EU-funded Human Brain Project based in Lausanne to pilot a data-sharing platform for the European consortia of InTBIR (CREACTIVE and CENTER-TBI). This led to a Memorandum of Association as a Partnering Project with Subproject 8 of HBP/Medical Informatics Platform. At the time of submission of the present Dissemination report, the data sharing platform, following various tests, was almost ready for federated data sharing.

The first use case to be implemented with the federated data sharing platform will be to combine CREACTIVE and CENTER-TBI data to validate the three IMPACT (IMPACT Core, IMPACT Extended and IMPACT Lab) models in a population large enough to be stratified for validation in relevant subgroups. A common series of metadata agreed on with the team from CENTER TBI will be incorporated as the first step towards permitting joint data analyses, validating the Core IMPACT score as the starting analysis.

At the federated level, researchers could investigate how data sharing among the centres participating in the International Initiative for Traumatic Brain Research (InTBIR) can contribute to create use cases or pilot projects to answer common research questions.

This work will continue for 12 months after the end of the CREACTIVE funding period through the above-mentioned Infrastructure Voucher programme promoted by HBP, giving free access to HBP/MIP services and engineering/development support.

Imperial College London

A collaboration to exploit CREACTIVE data started with Imperial College London in the second reporting period and was further consolidated across the remaining life of the project through the NEURON ERA-NET project, BIO-AX-TBI (*Developing and validating blood and imaging BIOmarkers of AXonal injury following Traumatic Brain Injury*). The BIO-AX-TBI outputs will be used to select the plasma biomarkers of axonal injury that best predict clinical outcome. These biomarkers will be validated by exploiting a large sample (approx. N=1000) of moderate-to-severe TBI patients collected within the CREACTIVE project. In addition, the relationship between the CT head scan appearances and plasma biomarkers will be investigated using machine-learning analysis to test whether CT head scans (collected under the CREACTIVE project) contain specific features of axonal injury and whether these features can be used to help predict outcome.

International Neuroinformatics Coordinating Facility

The CREACTIVE Consortium was invited to join a networking collaboration with The International Neuroinformatics Coordinating Facility (INCF) and to take part in applying for joint projects in the field of Traumatic Brain Injury research and management. The first joint proposal in the series was "*Connecting Global Neuroscience Initiatives to Advance Brain Health in Europe (CoGNITAB)*," submitted on 18 April, 2018, but not unfortunately selected for funding.

The CREACTIVE Coordinator, was an invited delegate a the INCF Workshop, "Towards alignment of brain initiatives in support of clinical data," held at the INCF buildings in Stockholm on 24-25 April, 2018.

Cyprus University

CREACTIVE started a collaboration with a **Neurorehabilitation research team based at Cyprus University, Nicosia** interested in exploiting CREACTIVE data and focusing on gender in access to services and care. The two forged ties with the University of Toronto to submit the proposal, "The Brain Injury Outcomes Network" to the 2018 GENDER-NET call. A grant was not awarded for this proposal. The two subsequently joined forces to collaborate on a PhD thesis exploiting CREACTIVE data. This included various teleconferences and an exchange visit by the clinical psychologist to the Ranica laboratory on 8-11 October, 2018.

CREACTIVE later collaborated with the same team in a proposal for a post-doc study under the ONISILOS scheme with the same Neurorehabilitation research team to exploit the CREACTIVE imaging repository beyond current funding. The proposed title is*, Integrating Brain Volume, Severity Indices, and Outcome Data from the CREACTIVE Project to Predict Brain Injury Recovery: A European Perspective – iC-BRAIN.*

National Enterprise for NanoScience and Nanotechnology (NEST) Laboratory

The CREACTIVE Consortium has been approached by the National Enterprise for NanoScience and Nanotechnology (NEST) Laboratory - Istituto Nanoscienze, CNR and Scuola Normale Superiore di Pisa, Italy. The NEST team has proposed to test a technique to assess 4-8 biomarkers at the bedside in the space of one hour. The extensive biomarker assays performed by the CREACTIVE Consortium on 2000 samples may provide some very interesting information on which biomarkers could be selected for this technique.

5. Conclusion: the future after CREACTIVE

The CREACTIVE study has achieved its specific objectives, further consolidated the European PROSAFE ICU network and amply met the challenge launched by InTBIR. CREACTIVE will leave an important legacy that will extend well beyond the formal EC funding period in the coming years, specifically in the following forms:

- A registry of 8000 patients with clinical data collection based on CDEs, facilitating data sharing
- A biological repository of over 2000 patients and an imaging repository with a **unique** dataset of over 1100 series for training and validation of machine-learning methods on TBI from CT imaging.
- A 3-level polytomous logistic regression prognostic model to assess the clinical effectiveness of clinical interventions.
- A federated data sharing platform to be used primarily for TBI but also for other neurological disorders

CREACTIVE data collection and analysis will not cease at the end of the EC funding period; on the contrary, the intention is to consolidate existing collaborations and seek new partnerships to fully exploit the work of 66 months.

Partners

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Budapest - **Hungary**

Medical University of Warsaw
Warsaw - **Poland**

General Hospital Novo Mesto
Novo Mesto - **Slovenia**

University Medical Center
Ljubljana - **Slovenia**

University of Nicosia - Nicosia General Hospital
Nicosia - **Cyprus**

Ben-Gurion University of the Negev
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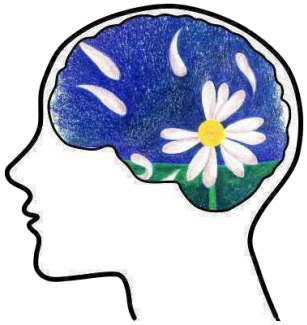


CREACTIVE

Collaborative REsearch on ACute Traumatic brain Injury in intensiVe care medicine in Europe

SEVENTH FRAMEWORK PROGRAMME

The project is supported by the European Commission through the Seventh Framework Programme under Grant Agreement no. 602714.

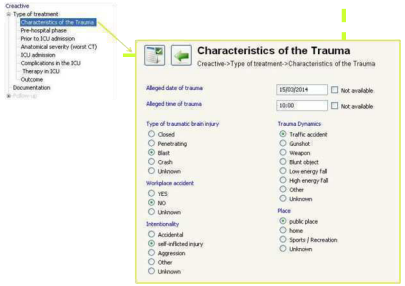
Aims of the study

- To consolidate the existing PROSAFE **network**, based on a prospective data collection in intensive care units (ICUs).
- To describe the **epidemiology** of moderate-to-severe TBI in 7 countries.
- To evaluate the consequences of TBI in **children**, through a multidimensional study of their outcomes.
- To establish a centralized **biobank** (blood and derived fluids, CSF) and a bank of clinical imaging for patients with TBI.
- To build a **prognostic model** based on clinical and biological data to predict short and medium term outcomes of TBI patients.
- To identify the most **effective clinical interventions** for optimally treating TBI patients.
- To recognize **centres of excellence** in treating TBI patients.
- To share data with other international research groups adhering to the InTBIR network.

The project involves 7 partners from Cyprus, Greece, Hungary, Israel, Italy, Poland and Slovenia.

CREACTIVE started on 1st October, 2013 and will run until 30th September, 2018.

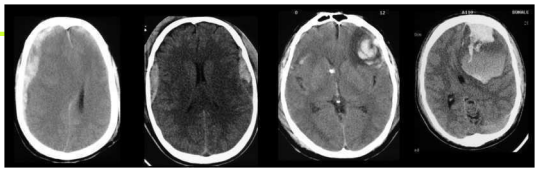
All ICUs already participating in the PROSAFE project and hospitalized patients with traumatic brain injury are invited to take part in **CREACTIVE**. For each patient with TBI, the centres have to fill out the case report form, which is already part of the PROSAFE database.



Follow-up will be performed six months after the trauma event, and will be two-tiered:

1. by telephone call for all patients;
2. by full patient examination to be performed in a selected subgroup of ICUs only.

In a subset of ICUs, **clinical images** carried out during routine clinical practice will be collected and centralized for all recruited patients. Images will undergo computer analysis, with a view to developing automatic or semi-automatic reading systems, thereby facilitating evaluation of the brain injury.

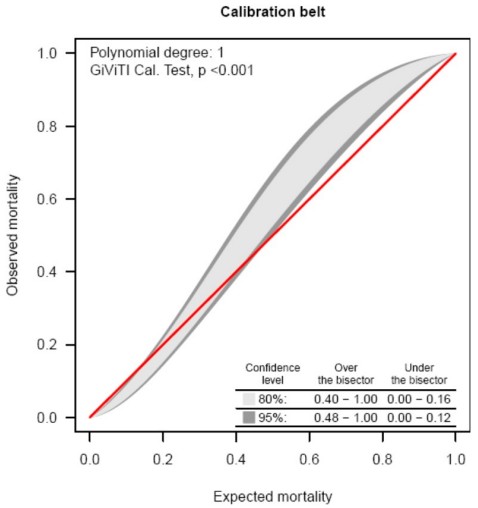


Biological samples will be collected and centralized in a subset of ICUs for phenotypic biomarker analysis. The choice of markers to be studied will be made after analysis of the images has suggested the most promising pathophysiological process to investigate.

Analysis

An annual report of the results will be produced in both aggregate and customized form for each participating centre. This will enable the centres to compare their data with those of the entire data set . Accordingly, different quality indicators will be developed (SMR, Calibration Belt, VLAD) in order to statistically adjust comparisons for differences in patient severity. An analysis plan based on the propensity score will be used to identify the most effective therapeutic interventions.

Based on the data collected, it is expected to enrol 7000 patients with moderate-to-severe traumatic brain injury in approximately 125 units, of which at least 80 Italian, by the end of the study, scheduled for September 2018.



GiViTI calibration belt to evaluate and develop prognostic models with a dichotomous outcome

GiViTI

Gruppo Italiano per la Valutazione degli Interventi In Terapia Intensiva

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Report
CREACTIVE project

Year 2017

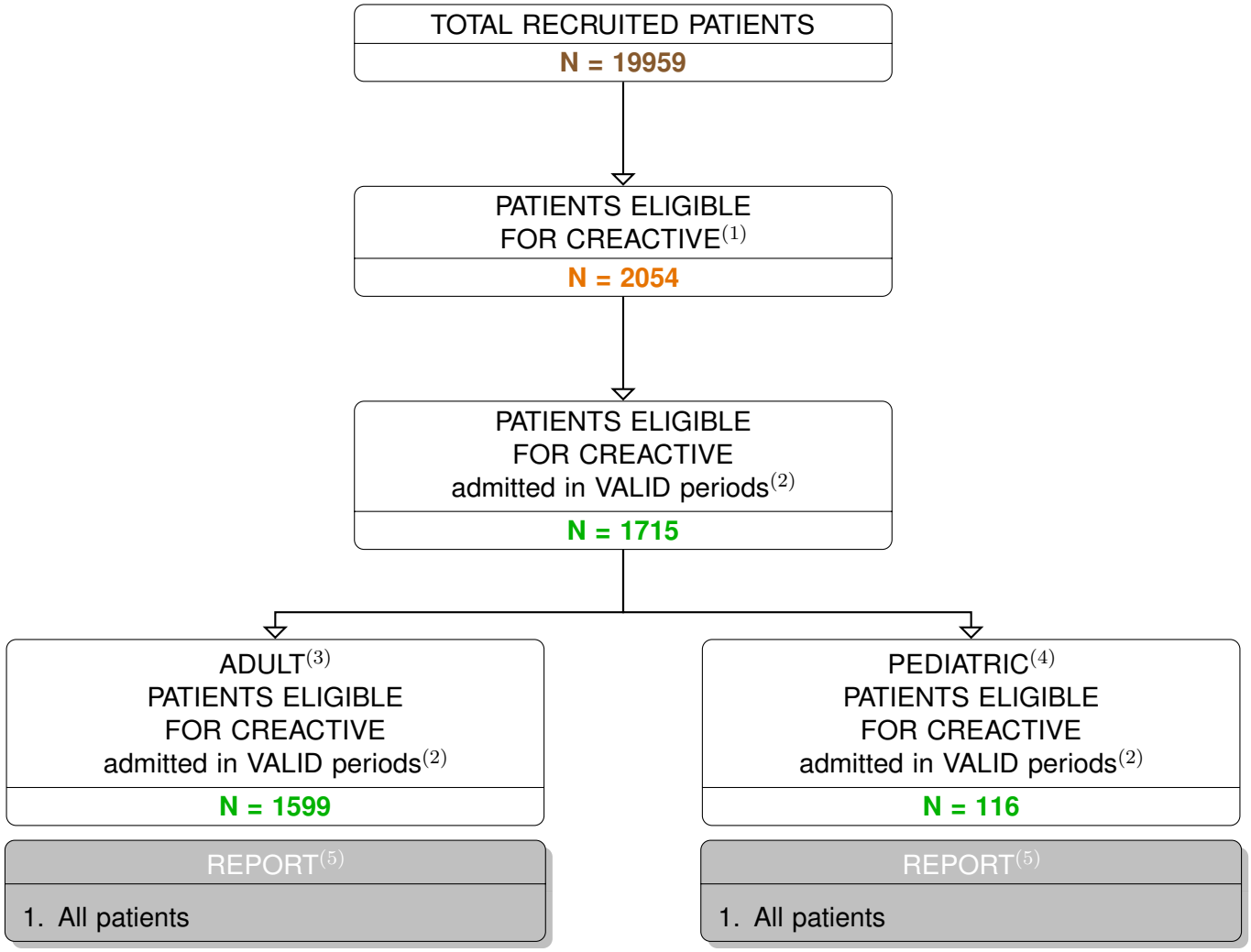
Overall population (51 ICUs)

Project participation*

Nation	ICUs	Adult Patients	Pediatric Patients	TBI Adult Patients	TBI Pediatric Patients	VALID TBI Adult Patients	VALID TBI Pediatric Patients
Cyprus	1	649	5	46	0	46	0
Greece	4	638	98	64	6	57	6
Hungary	4	884	17	284	6	220	5
Israel	2	47	1288	0	45	0	34
Italy	31	13187	887	1150	72	910	62
Poland	7	1135	194	181	9	175	9
Slovenia	2	928	2	191	0	191	0
Total	51	17468	2491	1916	138	1599	116
		19959		2054		1715	

*Only the ICUs providing valid data are included in the analysis.

Overall population with valid data (51 ICUs) - **Year 2017**
Study flow-chart



(1) Patients with traumatic brain injury are eligible to participate in CREACTIVE (the petal is not activated for patients with maxillofacial fractures only).
(2) Periods are considered VALID when the % of complete data for core and petal are over the thresholds.
(3) Patients older than 17 years are considered ADULT patients.
(4) Patients under 17 years of age are considered PEDIATRIC patients.
(5) Statistics are only provided for categories of patients composed of at least 5 subjects.

General report - **Year 2017**
Characteristics on admission - Adult patients

Patients (N): 1599

Sex	N	%
Male	1210	75.7
Female	388	24.3
Missing	1	

Age (years)	N	%
17-45	538	33.6
46-65	429	26.8
66-75	255	15.9
>75	377	23.6
Missing	0	
Mean	55.7	
SD	21.1	
Median	58	
Q1−Q3	38−75	
Min−Max	17−97	

Race	N	%
White European	1536	96.2
White African	10	0.6
Black Afro-american	10	0.6
Asian	13	0.8
Arab	8	0.5
Nomad	0	0.0
Unknown	20	1.3
Missing	2	

Marital status:	N	%
Married	535	33.5
Unmarried / Single	327	20.5
Separated / Divorced	46	2.9
Cohabiting	52	3.3
Widowed	109	6.8
Unknown	528	33.1
Missing	2	

Education level	N	%
No schooling	23	1.4
Primary school/ Elementary school	300	18.8
High school diploma	269	16.8
University degree	58	3.6
Unknown	947	59.3
Missing	2	

Occupational status:	N	%
Worker	422	26.4
Student	450	28.2
Homemaker	22	1.4
Retired	67	4.2
Unemployed / Looking for work	70	4.4
Disabled / Not applicable / Sheltered employment	20	1.3
Unknown	546	34.2
Missing	2	

Body mass Index (BMI)	N	%
Underweight	55	3.5
Normal	797	50.4
Overweight	581	36.7
Obese	149	9.4
Missing	17	

Comorbidities	N	%
No	668	41.8
Yes	931	58.2
Missing	0	

Comorbidities (top 10)	N	%
Hypertension	558	34.9
Alcohol addiction	167	10.4
Arrhythmia	157	9.8
Antiplatelet therapy	134	8.4
Diabetes Type II without insulin tr.	130	8.1
Myocardial infarction	112	7.0
Cerebrovascular disease	105	6.6
Drug-induced coagulopathy	95	5.9
NYHA class II-III	77	4.8
Moderate COPD	66	4.1
Missing	0	

Multiple trauma	N	%
No	879	55.0
Yes	720	45.0
Missing	0	

Trauma (anatomical districts)	N	%
Spine	318	19.9
Vertebral fracture, without deficit	271	16.9
Tetraplegia	13	0.8
Cervical injury, incomplete deficit	11	0.7
Chest	497	31.1
Other injuries of the chest	257	16.1
Traum. haemothorax/pneumothorax	213	13.3
Severe lung contusion/laceration	161	10.1
Abdomen	134	8.4
Minor injuries of the abdomen	41	2.6
Liver: Moderate-Severe laceration	37	2.3
Spleen: Moderate-Severe laceration	30	1.9
Pelvis/bone/joint & muscle	333	20.8
Long bone fracture	251	15.7
Multiple fracture of the pelvis	123	7.7
Very severe or open fracture of the pelvis	13	0.8
Major vessels injury	33	2.1
Neck vessels: dissection/transection	13	0.8
Proximal limbs vessels: transection	8	0.5
Aorta: rupture/dissection	7	0.4
Miscellaneous	3	0.2
Inhalation injury	2	0.1
Burns (>30% BSA)	1	0.1
Missing	0	

General report - **Year 2017**
Timing of admission in ICU - Adult patients

Stay before ICU (days)	
Mean	0.8
SD	5.0
Median	0
Q1−Q3	0−1
Missing	0

Source of admission	N	%
Same hospital	1293	80.9
Other hospital	303	18.9
Long-term chronic care hospital	2	0.1
Directly from the community	1	0.1
Missing	0	

Ward of admission **Same hospital** (N=1293)	N	%
Medical ward	23	1.8
Surgical ward	258	20.0
Emergency room	941	72.8
Other ICU	39	3.0
High dependency care unit	32	2.5
Missing	0	

Ward of admission **Other hospital** (N=303)	N	%
Medical ward	21	6.9
Surgical ward	26	8.6
Emergency room	220	72.6
Other ICU	32	10.6
High dependency care unit	4	1.3
Missing	0	

Reason for transfer from **Other ICU** (N=71)	N	%
Specialist expertise	32	45.1
Step-up care	24	33.8
Logistical/organizational reasons	15	21.1
Step-down care	0	0.0
Missing	0	

Access type	N	%
Primary	1296	81.1
Secondary	303	18.9
Within 48 hours	257	88.6
Over 48 hours	33	11.4
Missing	13	
Missing	0	

Time of trauma available	N	%
No	460	28.8
Yes	1137	71.2
Missing	2	

Hours between trauma and admission in ICU
Time of trauma available (N=1137)

Mean	13.2
SD	25.2
Median	5
Q1−Q3	3−9
Min−Max	0−171
Missing	0

Hours between trauma and admission in ICU
Time of trauma available - Same hospital (N=967)

Mean	12.9
SD	25.5
Median	4
Q1−Q3	3−8
Min−Max	0−171
Missing	0

Hours between trauma and admission in ICU
Time of trauma available - Other hospital (N=168)

Mean	15.0
SD	23.2
Median	7
Q1−Q3	4.8−15
Min−Max	0−169
Missing	0

Hours between trauma and admission in ICU
Time of trauma available - Same hospital - Emergency room (N=748)

Mean	8.2
SD	19.0
Median	4
Q1−Q3	2−6
Min−Max	0−171
Missing	0

Hours between trauma and admission in ICU
Time of trauma available - Other hospital - Emergency room (N=131)

Mean	12.0
SD	17.6
Median	6
Q1−Q3	4−11.5
Min−Max	0−122
Missing	0

General report - **Year 2017**
Characteristics of the trauma - Adult patients

Type of traumatic brain injury	N	%
Penetrating	55	3.4
Closed	1521	95.4
Unknown	19	1.2
Missing	4	

Workplace accident	N	%
No	1432	89.8
Yes	112	7.0
Unknown	51	3.2
Missing	4	

Home/domestic accident	N	%
No	999	62.6
Yes	518	32.5
Unknown	78	4.9
Missing	4	

Road traffic incident	N	%
No	927	58.1
Yes	668	41.9
Missing	4	

Means of transport **Road traffic incident** (N=668)	N	%
Truck/bus	13	1.9
Car/van	191	28.6
Motorcycle	176	26.3
Bicycle	103	15.4
Pedestrian	168	25.1
Other	17	2.5
Missing	0	

Sport/recreational accident	N	%
No	1444	90.5
Yes	83	5.2
Unknown	68	4.3
Missing	4	

Intention	N	%
Accidental	1387	87.0
Self-inflicted injury	59	3.7
Violence	35	2.2
Other	7	0.4
Unknown	107	6.7
Missing	4	

Trauma Dynamics	N	%
High energy impact with helmet	159	10.0
High energy impact without helmet	634	39.7
Low energy impact with helmet	43	2.7
Low energy impact without helmet	581	36.4
Blunt object	36	2.3
Crush	17	1.1
Blast	0	0.0
Gunshot	17	1.1
Acceleration/deceleration	85	5.3
Unknown	86	5.4
Missing	4	

General report - **Year 2017**
Type of trauma - Adult patients

Type of lesion°	**Present [N (%)]**	**Main [N (%)]**
Diffuse Injury *	247 (15.4%)	148 (9.3%)
Focal Damage **	1336 (83.6%)	1136 (71.2%)
G: Traumatic subarachnoid haemorrhage	728 (45.5%)	263 (16.5%)
H: Skull fracture	601 (37.6%)	48 (3%)

Marshall Classification	N	%
Diffuse Injury I (no visible pathology)	171	10.7
(D-II) Diffuse injury II	543	34.0
Diffuse Injury III (edema)	156	9.8
Diffuse Injury IV (shift>5mm)	59	3.7
(5-EML) Evacuated mass lesion	504	31.6
Traumatic intraparenchymal hemorrhage	46	9.6
Contusion and/ or brain laceration	43	9.0
Extradural or epidural hematoma	96	20.1
Traumatic subdural hematoma	293	61.3
(6-NEML) Not Evacuated mass lesion	162	10.2
Traumatic intraparenchymal hemorrhage	37	25.5
Contusion and/ or brain laceration	45	31.0
Extradural or epidural hematoma	3	2.1
Traumatic subdural hematoma	60	41.4
Missing	4	

Main lesion: DIFFUSE INJURY (N): 148

Diffuse Injury	N main	With focal	With **G**	With focal+**G**
A: Traumatic diffuse injury without oedema	61	5	12	3
B: Traumatic diffuse injury with oedema	87	22	8	30

Petechiae	N	%
No	45	30.4
Yes	103	69.6
Missing	0	

Midline shift>5 mm	N	%
No	122	82.4
Yes	26	17.6
Missing	0	

Cistern conditions	N	%
Normal	81	54.7
Compressed or distorted	42	28.4
Absent	25	16.9
Missing	0	

Presence of focal damage	N	%
No	88	59.5
Yes	60	40.5
Missing	0	

Focal lesion

Presence of focal damage (N=60)	N	%
Traumatic Subdural haematoma	37	61.7
Cerebral contusion/laceration	32	53.3
Traumatic intraparenchymal bleeding	9	15.0
Extradural/epidural haematoma	6	10.0
Missing	0	

Lesion volume > 25ml (N=60)	N	%
No	47	78.3
Yes	13	21.7
Missing	0	

Evacuated mass (N=60)	N	%
No	50	83.3
Yes	10	16.7
Missing	0	

° Where both are present, the clinician is requested to select and indicate the main injury.
* Traumatic diffuse injury without oedema, Traumatic diffuse injury with oedema.
** Cerebral contusion/laceration, Extradural/epidural haematoma, Traumatic Subdural haematoma, Traumatic intraparenchymal bleeding.

General report - **Year 2017**
Type of trauma - Adult patients

Main lesion: FOCAL DAMAGE (N): 1136

Focal Injury	N main	With diffuse	With **G**	With diffuse+**G**
C: Cerebral contusion/laceration	382	11	142	18
D: Extradural/epidural haematoma	134	4	30	3
E: Traumatic Subdural haematoma	479	13	134	11
F: Traumatic intraparenchymal bleeding	141	4	53	8

Lesion volume > 25ml	N	%
No	613	54.0
Yes	523	46.0
Missing	0	

Evacuated mass	N	%
No	658	57.9
Yes	478	42.1
Missing	0	

Petechiae	N	%
No	704	62.0
Yes	432	38.0
Missing	0	

Midline shift>5 mm	N	%
No	639	56.2
Yes	497	43.8
Missing	0	

Cistern conditions	N	%
Normal	513	45.2
Compressed or distorted	560	49.3
Absent	63	5.5
Missing	0	

Presence of diffuse injury	N	%
No	1064	93.7
Yes	72	6.3
Missing	0	

FOCAL DAMAGE (as main or compresent) (N): 1336

Lesion volume > 25ml	N	%
No	774	58.1
Yes	559	41.9
Missing	3	

Evacuated mass	N	%
No	829	62.2
Yes	504	37.8
Missing	3	

Midline shift>5 mm	N	%
No	794	59.6
Yes	539	40.4
Missing	3	

Cistern conditions	N	%
Normal	624	46.8
Compressed or distorted	624	46.8
Absent	85	6.4
Missing	3	

FOCAL DAMAGE (as main or compresent) with evacuated mass (N): 504

Lesion volume > 25ml	N	%
No	107	21.2
Yes	397	78.8
Missing	0	

Midline shift>5 mm	N	%
No	107	21.2
Yes	397	78.8
Missing	0	

Cistern conditions	N	%
Normal	93	18.5
Compressed or distorted	370	73.4
Absent	41	8.1
Missing	0	

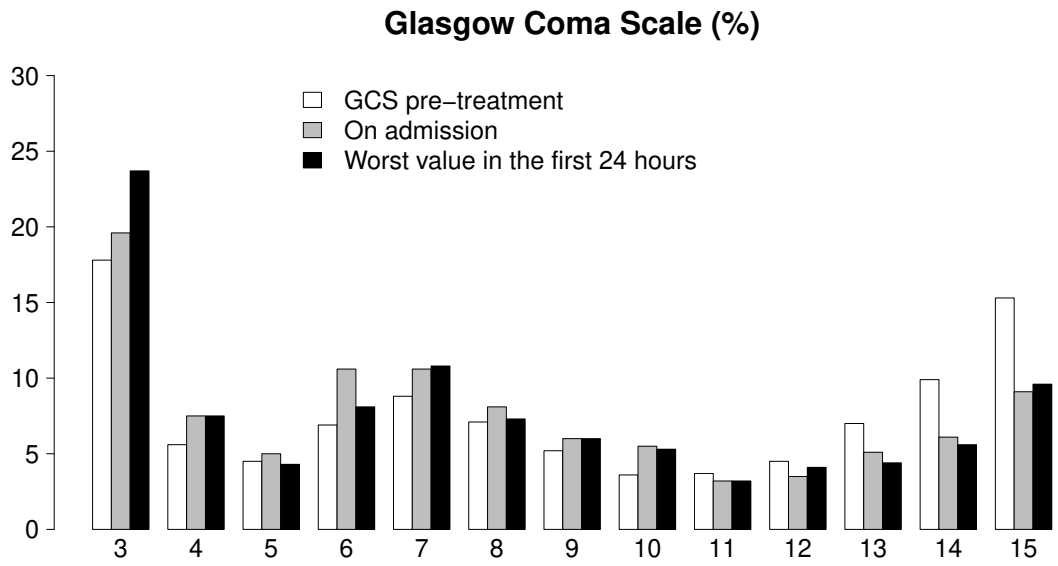
FOCAL DAMAGE (as main or compresent) without evacuated mass (N): 829

Lesion volume > 25ml	N	%
No	667	80.5
Yes	162	19.5
Missing	0	

Midline shift>5 mm	N	%
No	687	82.9
Yes	142	17.1
Missing	0	

Cistern conditions	N	%
Normal	531	64.1
Compressed or distorted	254	30.6
Absent	44	5.3
Missing	0	

General report - **Year 2017**
Glasgow Coma Scale - Adult patients



GCS pre-treatment	
Median	8
Q1−Q3	5−14
Missing	2

GCS (admission)	
Median	7
Q1−Q3	4−11
Not evaluable	517
Missing	1

Worst GCS (first 24 hours)	
Median	7
Q1−Q3	4−11
Not evaluable	628
Missing	1

GCS	GCSPre(N)	GCSPre(%)	GCSAdm(N)	GCSAdm(%)	GCSWorst24(N)	GCSWorst24(%)
3	284	17.8	212	19.6	230	23.7
4	90	5.6	81	7.5	73	7.5
5	72	4.5	54	5	42	4.3
6	110	6.9	115	10.6	79	8.1
7	141	8.8	115	10.6	105	10.8
8	114	7.1	87	8.1	71	7.3
9	83	5.2	65	6	58	6
10	57	3.6	59	5.5	51	5.3
11	59	3.7	35	3.2	31	3.2
12	72	4.5	38	3.5	40	4.1
13	112	7	55	5.1	43	4.4
14	158	9.9	66	6.1	54	5.6
15	245	15.3	98	9.1	93	9.6
Tot	**1597**	100	**1080**	100	**970**	100
3-8					600	61.9
9-13					223	23
14-15					147	15.2

Worst GCS during first 24h: best motor response	N	%
Obeys commands (6)	247	15.5
Localizes pain (5)	292	18.3
Withdraws to pain (4)	145	9.1
Flexion (abnormal) to pain (3)	68	4.3
Extension to pain (2)	81	5.1
None(1)	279	17.5
Not available	486	30.4
Missing	1	

GCS trend in 48h **Available information** (N=1066)	N	%
GCS 3 stable	103	9.7
GCS from 3 to 4-8	31	2.9
GCS from 3 to $>$ 8	23	2.2
GCS from 4-8 to 3	54	5.1
GCS 4-8 stable	147	13.8
GCS from 4-8 to $>$ 8	113	10.6
GCS from $>$ 8 to 3	50	4.7
GCS from $>$ 8 to 4-8	120	11.3
GCS $>$ 8 stable	425	39.9
Missing	0	

Availability of the pre-ICU systolic blood pressure value	N	%
No	429	26.9
Yes	1166	73.1
Missing	4	

Clinically relevant hypotension	N	%
No	1198	75.1
Yes	246	15.4
Not available	151	9.5
Missing	4	

(Lowest) systolic blood pressure value	
Mean	119.8
SD	35.1
Median	120
Q1−Q3	97.8−140
Min−Max	20−260
Missing	0

Availability of pre-ICU hypoxia value	N	%
No	450	28.2
Yes	1145	71.8
Missing	4	

Clinically relevant hypoxia	N	%
No	1075	67.4
Yes	368	23.1
Not available	152	9.5
Missing	4	

(Lowest) peripheral oxygen saturation value	
Mean	93.5
SD	9.6
Median	96
Q1−Q3	92−98
Min−Max	10−100
Missing	0

Pupils in the emergency room GCS pre < 15 (N=1352)	N	%
Bilaterally reactive and/or miotic	901	66.7
Unilaterally dilated and non-reactive	279	20.7
Bilaterally dilated and non-reactive	119	8.8
Not assessable	20	1.5
Not available	31	2.3
Missing	2	

Hemoglobin ER (gr/dl)	
Mean	12.3
SD	2.3
Median	12.6
Q1−Q3	11−14
Min−Max	1−20
Not available	237
Missing	4

Blood glucose at ER (mg/dl)	
Mean	158.1
SD	63.9
Median	146
Q1−Q3	120−181
Min−Max	4−612
Not available	308
Missing	4

General report - **Year 2017**
Complications in the ICU - Adult patients

Neurological complications during the stay	N	%
No	779	48.7
Yes	819	51.3
A: Intracranial hypertension	494	31.0
B: Intracranial hypertension refractory or intractable	284	17.8
C: At least one episode of dilated pupils unreactive to light	352	22.1
D: Reduction of serum sodium	124	7.8
E: Post-surgical intracranial bleeding	24	1.5
F: Non-surgical intracranial bleeding	18	1.1
G: Seizures	54	3.4
H: Drowsiness/agitation/delirium	172	10.8
Missing	1	

Neurological complications during the stay (top 10)	N	%
ABC	162	10.1
H	119	7.4
A	116	7.3
C	81	5.1
AB	67	4.2
D	52	3.3
AC	44	2.8
G	22	1.4
AD	13	0.8
AH	13	0.8
Missing	1	

Other complications during the stay	N	%
Respiratory	201	12.6
Atelectasis	79	4.9
Pleural effusion	62	3.9
Pneumothorax/Pneumomediastinum	37	2.3
Aspiration pneumonia	34	2.1
Pulmonary embolism	13	0.8
Cardiovascular	155	9.7
Deep venous thrombosis	46	2.9
Acute severe arrhythmia: tachycardias	46	2.9
Cardiac arrest	30	1.9
Acute severe arrhythmia: bradycardias	14	0.9
Hypertensive crisis	10	0.6
Gastrointestinal and hepatic	43	2.7
Paralytic Ileus	17	1.1
Liver Dysfunction Syndrome	7	0.4
Gastrointestinal bleeding: upper tract	6	0.4
Acute bile-duct disease	5	0.3
Gastrointestinal bleeding: lower tract	3	0.2
Other	64	4.0
Metabolic disorder	36	2.3
Nephrourologic disease	8	0.5
Other disease	8	0.5
Fat embolism	2	0.1
Iatrogenic major vessels injury	2	0.1
Delayed spleen rupture	1	0.1
Extremity compartment syndrome (severe)	1	0.1
Infections	592	37.0
Pneumonia	280	17.5
L.R.T.I. other than pneumonia	154	9.6
NON-surgical urinary tract infection	65	4.1
Primary bacteraemia of unknown origin	39	2.4
Catheter-related bacteremia (CR-BSI)	36	2.3
F.U.O. fever of unknown origin	30	1.9
Upper respiratory tract infection	27	1.7
Clinical sepsis	18	1.1
Sinusitis	17	1.1
Post-surgical skin/soft tissue infection	13	0.8
Missing	1	

General report - **Year 2017**
Process indicators - Adult patients

ICP monitoring in Core	N	%
No	1134	70.9
Yes	465	29.1
Missing	0	

ICP monitoring in Core **Worst value in the first 24 hours <= 8** (N=600)	N	%
No	433	72.2
Yes	167	27.8
Missing	0	

Neurosurgical operation	N	%
No	918	57.5
Yes	679	42.5
Subdural haematoma evcuation	363	22.7
Extradural haematoma evcuation	103	6.4
Lobectomy or contusion removal	42	2.6
Primary decompression	152	9.5
Secondary decompression	44	2.8
Other neurosurgical procedure	159	10.0
Missing	2	

Hypothermia	N	%
No	1585	99.1
Yes	14	0.9
Missing	0	

External ventricular drainage without ICP monitoring	N	%
No	1576	98.6
Yes	23	1.4
Missing	0	

External ventricular drainage with ICP monitoring	N	%
No	1493	93.4
Yes	106	6.6
Missing	0	

Barbiturate infusion for refractory ICP	N	%
No	1497	93.9
Yes	98	6.1
Missing	4	

Hyperventilation paCO2<25 mmHg	N	%
No	1546	96.9
Yes	49	3.1
Missing	4	

Indomethacin	N	%
No	1588	99.6
Yes	7	0.4
Missing	4	

Mannitol (multiple doses)	N	%
No	1224	76.7
Yes	371	23.3
Missing	4	

Hypertonic saline	N	%
No	1423	89.2
Yes	172	10.8
Missing	4	

Osmotic therapy	N	%
No	1150	72.1
Yes	445	27.9
Missing	4	

Sedation/analgesia	N	%
No	1081	67.8
Yes	514	32.2
Missing	4	

Propofol infusion for refractory ICP	N	%
No	1412	88.5
Yes	183	11.5
Missing	4	

Vasoconstrictor drugs **Vasoactive drugs in Core** (N=971)	N	%
No	332	34.3
Yes	635	65.7
Missing	4	

Therapy level	N	%
None	714	44.7
Standard	393	24.6
Intermediate	221	13.8
Extreme - medical	227	14.2
Extreme - surgical	44	2.8
Missing	0	

ICU stay (days)	
Mean	11.5
SD	12.6
Median	7
Q1−Q3	3−16
Min−Max	1−152
Missing	1

Hospital stay (days) [1],[2]	
Mean	22.8
SD	26.9
Median	15
Q1−Q3	6−29
Min−Max	0−248
Missing	5

ICU mortality [3]	N	%
Alive	1214	76.1
Dead	381	23.9
Missing	4	

Hospital mortality [1],[3]	N	%
Alive	1126	70.8
Dead	465	29.2
Missing	5	

Cause of death [4] **Dead** (N=375)	N	%
MOF	56	14.9
Comorbidities	29	7.7
Cerebral	271	72.3
Hemorrhagic	12	3.2
Not determined	7	1.9
Missing	0	

Last hospital mortality [1]	N	%
Alive	1091	68.8
Dead	494	31.2
Missing	11	

Outcome at discharge from ICU [5] **Alive** (N=1220)	N	%
Cannot follow simple commands	377	31.0
Can follow simple commands	841	69.0
Missing	2	

Does the patient have language problems? **Can follow simple commands** (N=841)	N	%
No	528	62.8
Si	216	25.7
Not assessable	97	11.5
Missing	0	

Does the patient have motor problems? **Alive** (N=1220)	N	%
No	627	51.5
Yes	591	48.5
Missing	2	

Is the patient oriented in at least one of the following dimensions: space, time, person, context? **Can follow simple commands** (N=841)	N	%
No	245	29.1
Yes	552	65.6
Unknown	44	5.2
Missing	0	

(1) Statistics calculated after excluding readmissions (N = 1596).
(2) Days between admission to ICU and discharge from hospital.
(3) Patients discharged in a preterminal condition (N = 6) were calculated among the deceased.
(4) Excluding patients discharged in a preterminal condition.
(5) Including patients discharged in a preterminal condition.

General report - **Year 2017**
Characteristics on admission - Pediatric patients

Patients (N): 116

Sex	N	%
Male	84	72.4
Female	32	27.6
Missing	0	

Age	N	%
Newborn (0-4 weeks)	0	0.0
1-6 months	0	0.0
6-12 months	6	5.2
12-24 months	7	6.0
2-4 years	13	11.2
5-8 years	27	23.3
9-16 years	63	54.3
Missing	0	
Mean	9.3	
SD	5.3	
Median	9	
Q1−Q3	5−15	
Min−Max	0−16	

Race	N	%
White European	54	67.5
White African	5	6.2
Black Afro-american	4	5.0
Asian	2	2.5
Arab	14	17.5
Nomad	0	0.0
Unknown	1	1.2
Missing	36	

Weight (kg)
Newborns (N=0)

Mean	
SD	
Median	
Q1−Q3	
Missing	0

Gestational age
Newborns (N=0)

	N	%
At term	0	0.0
Not at term	0	0.0
Missing	0	

Comorbidities	N	%
No	113	97.4
Yes	3	2.6
Missing	0	

Comorbidities (top 10)	N	%
Asthma	1	0.9
Coagulation disorder	1	0.9
Endocrine-metabolic diseases	1	0.9
-	0	0.0
-	0	0.0
-	0	0.0
-	0	0.0
-	0	0.0
-	0	0.0
-	0	0.0
Missing	0	

Multiple trauma	N	%
No	77	66.4
Yes	39	33.6
Missing	0	

Trauma (anatomical districts)	N	%
Spine	9	7.8
Vertebral fracture, without deficit	6	5.2
Cervical injury, incomplete deficit	2	1.7
Paraplegia	1	0.9
Chest	18	15.5
Other injuries of the chest	10	8.6
Traum. haemothorax/pneumothorax	7	6.0
Severe lung contusion/laceration	4	3.4
Abdomen	12	10.3
Spleen: Moderate-Severe laceration	4	3.4
Liver: Moderate-Severe laceration	3	2.6
Kidney: Rupture/laceration	3	2.6
Pelvis/bone/joint & muscle	25	21.6
Long bone fracture	23	19.8
Multiple fracture of the pelvis	2	1.7
Massive crush/amputation	2	1.7
Major vessels injury	0	0.0
-	0	0.0
-	0	0.0
-	0	0.0
Miscellaneous	0	0.0
-	0	0.0
-	0	0.0
Missing	0	

General report - **Year 2017**
Timing of admission in ICU - Pediatric patients

Previous ICU admissions	N	%
None	98	84.5
<=2	5	4.3
>2	1	0.9
Unknown	12	10.3
Missing	0	

Stay before ICU (days)	
Mean	0.3
SD	0.6
Median	0
Q1−Q3	0−1
Missing	0

Source of admission	N	%
Same hospital	82	70.7
Other hospital	29	25.0
Long-term chronic care hospital	0	0.0
Directly from the community	5	4.3
Missing	0	

Ward of admission **Same hospital** (N=82)	N	%
Medical ward	1	1.2
Surgical ward	11	13.4
Emergency room	65	79.3
Other ICU	5	6.1
High dependency care unit	0	0.0
Missing	0	

Ward of admission **Other hospital** (N=29)	N	%
Medical ward	2	6.9
Surgical ward	0	0.0
Emergency room	25	86.2
Other ICU	2	6.9
High dependency care unit	0	0.0
Missing	0	

Reason for transfer from **Other ICU** (N=7)	N	%
Specialist expertise	3	42.9
Step-up care	3	42.9
Logistical/organizational reasons	0	0.0
Step-down care	1	14.3
Missing	0	

Access type	N	%
Primary	87	75.0
Secondary	29	25.0
Within 48 hours	27	96.4
Over 48 hours	1	3.6
Missing	1	
Missing	0	

Time of trauma available	N	%
No	27	23.3
Yes	89	76.7
Missing	0	

Hours between trauma and admission in ICU *Time of trauma available* (N=89)	
Mean	6.8
SD	9.3
Median	5
Q1−Q3	3−7
Min−Max	0−73
Missing	0

Hours between trauma and admission in ICU *Time of trauma available - Same hospital (N=65)*	
Mean	7.0
SD	10.7
Median	5
Q1−Q3	2−7
Min−Max	0−73
Missing	0

Hours between trauma and admission in ICU *Time of trauma available - Other hospital (N=20)*	
Mean	6.8
SD	3.1
Median	6
Q1−Q3	4−8.5
Min−Max	4−14
Missing	0

Hours between trauma and admission in ICU *Time of trauma available - Same hospital - Emergency room (N=57)*	
Mean	4.5
SD	3.3
Median	4
Q1−Q3	2−6
Min−Max	1−19
Missing	0

Hours between trauma and admission in ICU *Time of trauma available - Other hospital - Emergency room (N=20)*	
Mean	6.8
SD	3.1
Median	6
Q1−Q3	4−8.5
Min−Max	4−14
Missing	0

General report - **Year 2017**
Characteristics of the trauma - Pediatric patients

Type of traumatic brain injury	N	%
Penetrating	4	3.4
Closed	110	94.8
Unknown	2	1.7
Missing	0	

Workplace accident	N	%
No	115	99.1
Yes	1	0.9
Unknown	0	0.0
Missing	0	

Home/domestic accident	N	%
No	88	75.9
Yes	27	23.3
Unknown	1	0.9
Missing	0	

Road traffic incident	N	%
No	54	46.6
Yes	62	53.4
Missing	0	

Means of transport		
Road traffic incident (N=62)	N	%
Truck/bus	0	0.0
Car/van	22	35.5
Motorcycle	10	16.1
Bicycle	11	17.7
Pedestrian	16	25.8
Other	3	4.8
Missing	0	

Sport/recreational accident	N	%
No	92	79.3
Yes	23	19.8
Unknown	1	0.9
Missing	0	

Intention	N	%
Accidental	108	93.1
Self-inflicted injury	4	3.4
Violence	2	1.7
Other	0	0.0
Unknown	2	1.7
Missing	0	

Trauma Dynamics	N	%
High energy impact with helmet	8	6.9
High energy impact without helmet	55	47.4
Low energy impact with helmet	0	0.0
Low energy impact without helmet	42	36.2
Blunt object	4	3.4
Crush	2	1.7
Blast	0	0.0
Gunshot	0	0.0
Acceleration/deceleration	4	3.4
Unknown	2	1.7
Missing	0	

General report - **Year 2017**
Type of trauma - Pediatric patients

Type of lesion°	**Present [N (%)]**	**Main [N (%)]**
Diffuse Injury *	30 (25.9%)	24 (20.7%)
Focal Damage **	81 (69.8%)	68 (58.6%)
G: Traumatic subarachnoid haemorrhage	30 (25.9%)	13 (11.2%)
H: Skull fracture	55 (47.4%)	11 (9.5%)

Marshall Classification	N	%
Diffuse Injury I (no visible pathology)	21	18.1
(D-II) Diffuse injury II	46	39.7
Diffuse Injury III (edema)	13	11.2
Diffuse Injury IV (shift>5mm)	9	7.8
(5-EML) Evacuated mass lesion	27	23.3
Traumatic intraparenchymal hemorrhage	1	4.3
Contusion and/ or brain laceration	3	13.0
Extradural or epidural hematoma	13	56.5
Traumatic subdural hematoma	6	26.1
(6-NEML) Not Evacuated mass lesion	0	0.0
Traumatic intraparenchymal hemorrhage	0	0.0
Contusion and/ or brain laceration	0	0.0
Extradural or epidural hematoma	0	0.0
Traumatic subdural hematoma	0	0.0
Missing	0	

Main lesion: DIFFUSE INJURY (N): 24

Diffuse Injury	N main	With focal	With **G**	With focal+**G**
A: Traumatic diffuse injury without oedema	10	1	1	0
B: Traumatic diffuse injury with oedema	14	4	2	1

Petechiae	N	%
No	7	29.2
Yes	17	70.8
Missing	0	

Midline shift>5 mm	N	%
No	19	79.2
Yes	5	20.8
Missing	0	

Cistern conditions	N	%
Normal	13	54.2
Compressed or distorted	9	37.5
Absent	2	8.3
Missing	0	

Presence of focal damage	N	%
No	18	75.0
Yes	6	25.0
Missing	0	

Focal lesion

Presence of focal damage (N=6)	N	%
Traumatic Subdural haematoma	3	50.0
Traumatic intraparenchymal bleeding	3	50.0
Cerebral contusion/laceration	2	33.3
Extradural/epidural haematoma	1	16.7
Missing	0	

Lesion volume > 25ml § (N=6)	N	%
No	5	83.3
Yes	1	16.7
Missing	0	

Evacuated mass (N=6)	N	%
No	3	50.0
Yes	3	50.0
Missing	0	

° Where both are present, the clinician is requested to select and indicate the main injury.
* Traumatic diffuse injury without oedema, Traumatic diffuse injury with oedema.
** Cerebral contusion/laceration, Extradural/epidural haematoma, Traumatic Subdural haematoma, Traumatic intraparenchymal bleeding.
§ Only for > 10 years old.

General report - **Year 2017**
Type of trauma - Pediatric patients

Main lesion: FOCAL DAMAGE (N): 68

Focal Injury	N main	With diffuse	With **G**	With diffuse+**G**
C: Cerebral contusion/laceration	20	1	5	1
D: Extradural/epidural haematoma	23	0	3	1
E: Traumatic Subdural haematoma	18	0	1	1
F: Traumatic intraparenchymal bleeding	7	1	0	0

Lesion volume > 25ml § (N=27)	N	%
No	21	77.8
Yes	6	22.2
Missing	0	

Evacuated mass	N	%
No	45	66.2
Yes	23	33.8
Missing	0	

Petechiae	N	%
No	44	64.7
Yes	24	35.3
Missing	0	

Midline shift>5 mm	N	%
No	51	75.0
Yes	17	25.0
Missing	0	

Cistern conditions	N	%
Normal	56	82.4
Compressed or distorted	10	14.7
Absent	2	2.9
Missing	0	

Presence of diffuse injury	N	%
No	63	92.6
Yes	5	7.4
Missing	0	

FOCAL DAMAGE (as main or compresent) (N): 81

Lesion volume > 25ml § (N=35)	N	%
No	28	80.0
Yes	7	20.0
Missing	0	

Evacuated mass	N	%
No	54	66.7
Yes	27	33.3
Missing	0	

Midline shift>5 mm	N	%
No	61	75.3
Yes	20	24.7
Missing	0	

Cistern conditions	N	%
Normal	60	74.1
Compressed or distorted	17	21.0
Absent	4	4.9
Missing	0	

FOCAL DAMAGE (as main or compresent) with evacuated mass (N): 27

Lesion volume > 25ml § (N=12)	N	%
No	5	41.7
Yes	7	58.3
Missing	0	

Midline shift>5 mm	N	%
No	14	51.9
Yes	13	48.1
Missing	0	

Cistern conditions	N	%
Normal	15	55.6
Compressed or distorted	9	33.3
Absent	3	11.1
Missing	0	

FOCAL DAMAGE (as main or compresent) without evacuated mass (N): 54

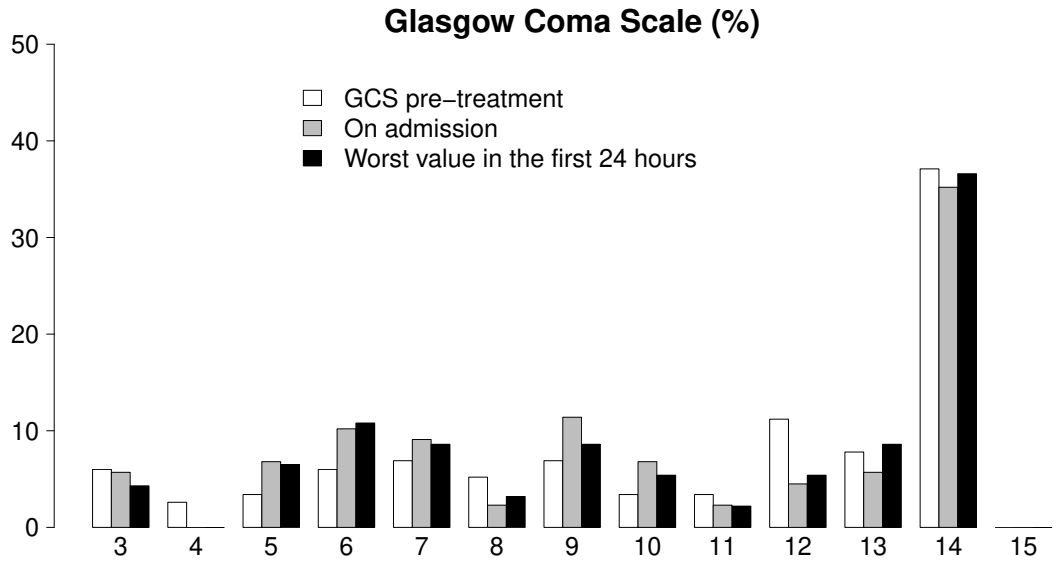
Lesion volume > 25ml § (N=23)	N	%
No	23	100.0
Yes	0	0.0
Missing	0	

Midline shift>5 mm	N	%
No	47	87.0
Yes	7	13.0
Missing	0	

Cistern conditions	N	%
Normal	45	83.3
Compressed or distorted	8	14.8
Absent	1	1.9
Missing	0	

§ Only for > 10 years old.

General report - **Year 2017**
Glasgow Coma Scale - Pediatric patients



GCS pre-treatment	
Median	12
Q1−Q3	7.8−14
Missing	0

GCS (admission)	
Median	10
Q1−Q3	7−14
Not evaluable	28
Missing	0

Worst GCS (first 24 hours)	
Median	12
Q1−Q3	7−14
Not evaluable	23
Missing	0

GCS	**GCSPre(N)**	**GCSPre(%)**	**GCSAdm(N)**	**GCSAdm(%)**	**GCSWorst24(N)**	**GCSWorst24(%)**
3	7	6	5	5.7	4	4.3
4	3	2.6	0	0	0	0
5	4	3.4	6	6.8	6	6.5
6	7	6	9	10.2	10	10.8
7	8	6.9	8	9.1	8	8.6
8	6	5.2	2	2.3	3	3.2
9	8	6.9	10	11.4	8	8.6
10	4	3.4	6	6.8	5	5.4
11	4	3.4	2	2.3	2	2.2
12	13	11.2	4	4.5	5	5.4
13	9	7.8	5	5.7	8	8.6
14	43	37.1	31	35.2	34	36.6
15	/	/	/	/	/	/
Tot	**116**	100	**88**	100	**93**	100
3-8					31	33.3
9-13					28	30.1
14					34	36.6

Worst GCS during first 24h: best motor response	N	%
Obeys commands (5)	51	44.0
Localizes pain (4)	27	23.3
Flexion to pain (3)	9	7.8
Extension to pain (2)	1	0.9
None(1)	5	4.3
Not available	23	19.8
Missing	0	

GCS trend in 48h **Available information** (N=91)	N	%
GCS 3 stable	4	4.4
GCS from 3 to 4-8	1	1.1
GCS from 3 to $>$ 8	0	0.0
GCS from 4-8 to 3	0	0.0
GCS 4-8 stable	7	7.7
GCS from 4-8 to $>$ 8	13	14.3
GCS from $>$ 8 to 3	0	0.0
GCS from $>$ 8 to 4-8	6	6.6
GCS $>$ 8 stable	60	65.9
Missing	0	

General report - **Year 2017**
Before admission to ICU - Pediatric patients

Availability of the pre-ICU systolic blood pressure value	N	%
No	48	41.4
Yes	68	58.6
Missing	0	

Clinically relevant hypotension	N	%
No	80	69.0
Yes	16	13.8
Not available	20	17.2
Missing	0	

(Lowest) systolic blood pressure value	
Mean	102.3
SD	28.1
Median	106.5
Q1−Q3	90−120
Min−Max	20−157
Missing	0

Availability of pre-ICU hypoxia value	N	%
No	41	35.3
Yes	75	64.7
Missing	0	

Clinically relevant hypoxia	N	%
No	66	56.9
Yes	33	28.4
Not available	17	14.7
Missing	0	

(Lowest) peripheral oxygen saturation value	
Mean	93.7
SD	15.0
Median	98
Q1−Q3	94.5−100
Min−Max	10−100
Missing	0

Pupils in the emergency room GCS pre < 14 (N=73)	N	%
Bilaterally reactive and/or miotic	57	80.3
Unilaterally dilated and non-reactive	5	7.0
Bilaterally dilated and non-reactive	6	8.5
Not assessable	0	0.0
Not available	3	4.2
Missing	2	

Hemoglobin ER (gr/dl)	
Mean	12.1
SD	1.9
Median	12.1
Q1−Q3	11−13.5
Min−Max	6.9−15.8
Not available	28
Missing	0

Blood glucose at ER (mg/dl)	
Mean	150.8
SD	41.3
Median	150
Q1−Q3	114.5−178.5
Min−Max	73−244
Not available	34
Missing	0

General report - **Year 2017**
Complications in the ICU - Pediatric patients

Neurological complications during the stay	N	%
No	79	68.1
Yes	37	31.9
A: Intracranial hypertension	33	28.4
B: Intracranial hypertension refractory or intractable	15	12.9
C: At least one episode of dilated pupils unreactive to light	12	10.3
D: Reduction of serum sodium	5	4.3
E: Post-surgical intracranial bleeding	0	0.0
F: Non-surgical intracranial bleeding	1	0.9
G: Seizures	6	5.2
H: Drowsiness/agitation/delirium	8	6.9
Missing	0	

Neurological complications during the stay (top 10)	N	%
A	10	8.6
ABC	7	6.0
AB	3	2.6
AH	3	2.6
H	2	1.7
ABCD	1	0.9
ABCG	1	0.9
ABDH	1	0.9
ABG	1	0.9
ABGH	1	0.9
Missing	0	

Other complications during the stay	N	%
Respiratory	15	12.9
Atelectasis	8	6.9
Aspiration pneumonia	3	2.6
Pleural effusion	3	2.6
Mild ARDS	2	1.7
Pneumothorax/Pneumomediastinum	2	1.7
Cardiovascular	1	0.9
Acute severe arrhythmia: bradycardias	1	0.9
-	0	0.0
-	0	0.0
-	0	0.0
-	0	0.0
Gastrointestinal and hepatic	0	0.0
-	0	0.0
-	0	0.0
-	0	0.0
-	0	0.0
-	0	0.0
Other	9	7.8
Metabolic disorder	5	4.3
Other disease	3	2.6
Nephrourologic disease	1	0.9
-	0	0.0
-	0	0.0
-	0	0.0
-	0	0.0
Infections	15	12.9
Pneumonia	8	6.9
L.R.T.I. other than pneumonia	3	2.6
Post-surgical skin/soft tissue infection	2	1.7
Catheter-related bacteremia (CR-BSI)	1	0.9
Catheter-related local infection	1	0.9
Post-surgical CNS infection	1	0.9
F.U.O. fever of unknown origin	1	0.9
Other fungal infections	1	0.9
NON-surgical urinary tract infection	1	0.9
-	0	0.0
Missing	0	

General report - **Year 2017**
Process indicators - Pediatric patients

ICP monitoring in Core	N	%
No	87	75.0
Yes	29	25.0
Missing	0	

ICP monitoring in Core **Worst value in the first 24 hours <= 8** (N=31)	N	%
No	19	61.3
Yes	12	38.7
Missing	0	

Neurosurgical operation	N	%
No	72	62.1
Yes	44	37.9
Subdural haematoma evcuation	10	8.6
Extradural haematoma evcuation	16	13.8
Lobectomy or contusion removal	1	0.9
Primary decompression	9	7.8
Secondary decompression	0	0.0
Other neurosurgical procedure	20	17.2
Missing	0	

Hypothermia	N	%
No	114	98.3
Yes	2	1.7
Missing	0	

External ventricular drainage without ICP monitoring	N	%
No	113	97.4
Yes	3	2.6
Missing	0	

External ventricular drainage with ICP monitoring	N	%
No	107	92.2
Yes	9	7.8
Missing	0	

Barbiturate infusion for refractory ICP	N	%
No	112	96.6
Yes	4	3.4
Missing	0	

Hyperventilation paCO2<25 mmHg	N	%
No	112	96.6
Yes	4	3.4
Missing	0	

Indomethacin	N	%
No	115	99.1
Yes	1	0.9
Missing	0	

Mannitol (multiple doses)	N	%
No	97	83.6
Yes	19	16.4
Missing	0	

Hypertonic saline	N	%
No	94	81.0
Yes	22	19.0
Missing	0	

Osmotic therapy	N	%
No	89	76.7
Yes	27	23.3
Missing	0	

Sedation/analgesia	N	%
No	78	67.2
Yes	38	32.8
Missing	0	

Propofol infusion for refractory ICP	N	%
No	98	84.5
Yes	18	15.5
Missing	0	

Vasoconstrictor drugs **Vasoactive drugs in Core** (N=27)	N	%
No	7	25.9
Yes	20	74.1
Missing	0	

Therapy level	N	%
None	74	63.8
Standard	9	7.8
Intermediate	14	12.1
Extreme - medical	19	16.4
Extreme - surgical	0	0.0
Missing	0	

ICU stay (days)	
Mean	4.9
SD	6.5
Median	2
Q1−Q3	1−6
Min−Max	1−44
Missing	0

Hospital stay (days) (1),(2)	
Mean	12.4
SD	12.4
Median	9
Q1−Q3	4.8−15
Min−Max	0−62
Missing	0

ICU mortality (3)	N	%
Alive	107	92.2
Dead	9	7.8
Missing	0	

Hospital mortality (1),(3)	N	%
Alive	107	92.2
Dead	9	7.8
Missing	0	

Cause of death (4) **Dead** (N=9)	N	%
MOF	1	11.1
Comorbidities	0	0.0
Cerebral	8	88.9
Hemorrhagic	0	0.0
Not determined	0	0.0
Missing	0	

Last hospital mortality (1)	N	%
Alive	107	92.2
Dead	9	7.8
Missing	0	

Outcome at discharge from ICU (5) **Alive >=4 years** (N=89)	N	%
Cannot follow simple commands	11	12.4
Can follow simple commands	78	87.6
Missing	0	

Does the patient have language problems? Can follow simple commands (>=4 years) (N=78)	N	%
No	69	88.5
Si	8	10.3
Not assessable	1	1.3
Missing	0	

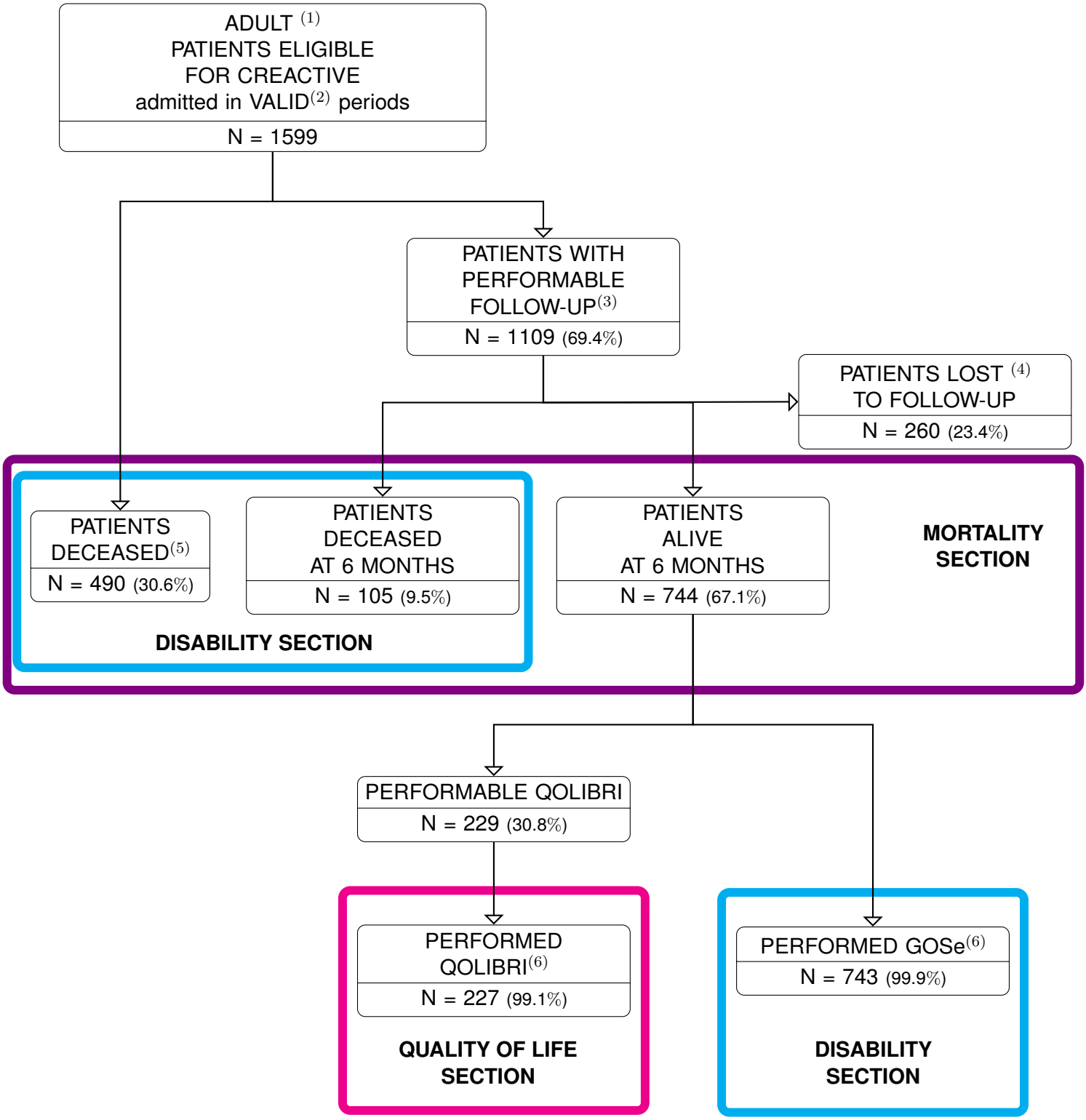
Does the patient have motor problems? Alive (>=4 years) (N=89)	N	%
No	71	79.8
Yes	18	20.2
Missing	0	

Is the patient oriented in at least one of the following dimensions: space, time, person, context? Can follow simple commands (>=4 years) (N=78)	N	%
No	36	46.2
Yes	41	52.6
Unknown	1	1.3
Missing	0	

(1) Statistics calculated after excluding readmissions (N = 116).
(2) Days between admission to ICU and discharge from hospital.
(3) Patients discharged in a preterminal condition (N = 0) were calculated among the deceased.
(4) Excluding patients discharged in a preterminal condition.
(5) Including patients discharged in a preterminal condition.

FOLLOW-UP

Overall population with valid data (47 ICUs) - **Year 2017**
Follow-up flow-chart - Adult patients



(1) Patients older than 17 years are considered ADULT patients.
(2) Periods are considered VALID when the % of complete data for core and petal are over the thresholds.
(3) Patients discharged alive > 6 months from the date of admission.
(4) This also includes patients declining to take part in the follow-up study or who are not contactable.
(5) Patients deceased in ICU or in hospital.
(6) Statistics are presented only for categories of patients represented by at least 5 subjects.

N.B. The % refers to the upper node in the flow chart.

General report - **Year 2017**
Follow-Up - 'Mortality' section: Mortality for main subgroups of patients - Adult patients

Patients (N): 1339

This section presents the mortality-related statistics.
Each of the tables provided is divided into two parts:

- the **first part** of each table (on the left-hand side, printed in black ink) refers to the ICU and the hospital mortality rates for each patient category.
  For example, 15.7% of the 538 patients aged between 17 and 45 years died in the ICU, while 16.7% died in hospital; 37.4% of the 377 patients aged over 75 years died in the ICU, while 54.4% died in hospital.
  This part of the table refers to all **adult CREACTIVE patients with valid data**.

- the **second part** of each table (on the right-hand side, printed in purple ink) refers instead to **adult CREACTIVE patients with valid data on whom we have 6-month outcome data** (alive or dead). The mortality rate at different time points (irrespective of the place of death - ICU, hospital, home) is shown for these patients: *within 4 days of the trauma event, between 4 and 7 days, between 8 and 30 days, and over 30 days*.
  For example, 427 of the valid adult CREACTIVE patients are aged between 17 and 45 years: of these, 10.4% died within 4 days of the trauma event, while the remaining 89.6% were still alive at that date. Accordingly, the only patients at risk of dying between 4 and 7 days are the ones still alive at day 4 *(427*0.896=383)*: 6.6% of these 383 died between 4 and 7 days. At this point, the only patients at risk of dying between 8 and 30 days are the ones who are still alive at day 8 *(i.e., 383*0.934=358)*; 5.1% of these died within 30 days.
  Hence, the sum of the percentages in each row does not produce 100%, since the denominator on which the rate is calculated varies for each column. To be precise, it consists of the number of subjects who are still alive at the start of the observation period of each column.

	All patients (N=1599)			Patients with follow-up (N=1339)				
Age	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
17-45	538	15.7	16.7	427	10.4	6.6	5.1	3.9
46-65	429	19.4	23.2	344	9.6	8.4	11.7	10.1
66-75	255	28.7	40.2	228	14.6	14.5	22.4	25.0
>75	377	37.4	54.4	340	20.1	18.9	34.9	32.4

	All patients (N=1599)			Patients with follow-up (N=1339)				
Comorbidities	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
Yes	931	29.0	40.0	814	14.5	14.3	22.9	22.2
No	668	16.8	18.7	525	11.7	6.7	6.8	3.8

	All patients (N=1599)			Patients with follow-up (N=1339)				
Source of admission	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
Same hospital	1293	24.3	30.9	1098	13.2	11.2	15.3	12.5
Other hospital	303	22.1	31.8	238	14.4	11.9	19.8	19.0
Long-term chronic care hospital	2	50.0	50.0	2	0.0	0.0	50.0	0.0
Directly from the community	1	0.0	0.0	1	0.0	0.0	0.0	0.0

† Mortality (%)
* from TBI

	All patients (N=1599)			Patients with follow-up (N=1339)				
Type of traumatic brain injury	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
Penetrating	55	55.6	60.0	52	34.6	32.4	26.1	11.8
Closed	1521	22.8	30.2	1273	12.2	10.7	16.0	13.5
Unknown	19	21.1	21.1	13	33.3	0.0	0.0	25.0

	All patients (N=1599)			Patients with follow-up (N=1339)				
Worst GCS (first 24 hours)	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
3-8	600	37.6	47.0	538	22.8	18.9	21.2	15.9
9-13	223	8.6	13.0	173	1.7	5.3	9.3	11.0
14-15	147	3.4	4.8	117	1.7	0.9	5.4	4.7
Not evaluable	628	21.0	28.6	511	10.1	9.3	17.5	15.6

	All patients (N=1599)			Patients with follow-up (N=1339)				
Worst GCS during first 24h: best motor response	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
Obeys commands (6)	247	4.0	5.7	194	1.0	1.6	5.9	6.8
Localizes pain (5)	292	10.0	15.9	241	1.2	6.3	10.4	13.6
Withdraws to pain (4)	145	16.7	28.3	122	4.1	11.1	17.3	19.8
Flexion (abnormal) to pain (3)	68	30.9	50.7	58	10.3	15.4	36.4	21.4
Extension to pain (2)	81	45.7	54.3	74	20.5	31.0	32.5	11.1
None(1)	279	57.6	64.4	260	43.2	31.3	21.8	20.3
Not available	486	20.6	28.3	390	9.1	7.7	19.0	13.5

	All patients (N=1599)			Patients with follow-up (N=1339)				
GCS trend in 48h	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
GCS 3 stable	103	70.6	73.5	97	52.6	37.0	20.7	17.4
GCS from 3 to 4-8	31	38.7	51.6	27	18.5	13.6	31.6	23.1
GCS from 3 to > 8	23	4.3	4.3	14	0.0	0.0	14.3	8.3
GCS from 4-8 to 3	54	63.0	66.7	50	52.0	33.3	25.0	16.7
GCS 4-8 stable	147	27.4	36.3	135	7.4	15.2	17.0	15.9
GCS from 4-8 to > 8	113	5.3	10.6	87	2.4	3.6	5.0	7.9
GCS from > 8 to 3	50	62.0	74.0	46	45.7	36.0	37.5	30.0
GCS from > 8 to 4-8	120	26.7	40.3	105	9.6	17.0	25.6	20.7
GCS > 8 stable	425	6.4	11.4	341	0.9	4.2	9.4	9.0

† Mortality (%)
* from TBI

General report - Year 2017
Follow-Up - 'Mortality' section: Mortality for main subgroups of patients - Adult patients

Clinically relevant hypotension	All patients (N=1599)			Patients with follow-up (N=1339)				
	N	† in ICU(%)	† in H(%)	N	† within 4 days(%)*	† 4-7 days(%)*	† 8-30 days(%)*	† over 30 days(%)*
No	1198	20.2	27.1	1013	9.9	9.8	14.9	12.0
Yes	246	38.2	46.3	209	26.9	17.8	18.4	19.6
Not available	151	29.8	38.3	116	18.1	14.7	24.7	21.3

Clinically relevant hypoxia	All patients (N=1599)			Patients with follow-up (N=1339)				
	N	† in ICU(%)	† in H(%)	N	† within 4 days(%)*	† 4-7 days(%)*	† 8-30 days(%)*	† over 30 days(%)*
No	1075	20.8	28.0	914	10.9	9.9	15.3	12.0
Yes	368	28.7	35.4	306	18.0	13.6	16.3	14.4
Not available	152	34.2	42.4	118	19.7	17.0	23.1	26.7

Pupils in the emergency room	All patients (N=1599)			Patients with follow-up (N=1339)				
	N	† in ICU(%)	† in H(%)	N	† within 4 days(%)*	† 4-7 days(%)*	† 8-30 days(%)*	† over 30 days(%)*
Bilaterally reactive and/or miotic	901	15.3	22.8	750	7.6	7.1	12.1	13.0
Unilaterally dilated and non-reactive	279	37.2	45.7	242	17.4	20.6	25.9	19.7
Bilaterally dilated and non-reactive	119	70.6	76.5	110	54.5	34.0	45.5	22.2
Not assessable	20	25.0	30.0	17	25.0	8.3	9.1	10.0
Not available	31	29.0	32.3	23	21.7	16.7	13.3	15.4

Anatomical severity (worst CT within 48 hours of admission)	All patients (N=1599)			Patients with follow-up (N=1339)				
	N	† in ICU(%)	† in H(%)	N	† within 4 days(%)*	† 4-7 days(%)*	† 8-30 days(%)*	† over 30 days(%)*
Diffuse Injury I (no visible pathology)	171	14.0	17.2	133	12.1	3.4	7.2	5.8
(D-II) Diffuse injury II	543	7.0	11.5	429	3.1	3.4	6.5	8.6
Diffuse Injury III (edema)	156	34.6	39.7	137	18.4	16.2	18.3	9.2
Diffuse Injury IV (shift>5mm)	59	50.8	64.4	53	32.1	33.3	33.3	12.5
(5-EML) Evacuated mass lesion	504	29.1	39.5	435	13.9	14.7	24.9	21.8
(6-NEML) Not Evacuated mass lesion	162	54.3	64.2	151	30.7	26.0	33.8	33.3

† Mortality (%)
* from TBI

Patients (N): 1338

	All patients (N=1305)		Alive patients (N=710)	
GOSe result :*	**N**	%	**N**	%
Deceased	594	45.5	-	-
Vegetative state	38	2.9	38	5.4
Severe disability LOWER LEVEL	194	14.9	194	27.3
Severe disability UPPER LEVEL	104	8.0	104	14.6
Moderate disability LOWER LEVEL	72	5.5	72	10.1
Moderate disability UPPER LEVEL	90	6.9	90	12.7
Good recovery LOWER LEVEL	93	7.1	92	13
Good recovery UPPER LEVEL	120	9.2	120	16.9

* patients with 'Pre-trauma disability' are not analyzed. **N=1305** patients, instead of 1338 are analyzed.

Disability for main subgroups of patients - N (%)

Age (years)	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
17-45	414	101 (24.4)	13 (3.1)	81 (19.6)	98 (23.7)	121 (29.2)
46-65	334	117 (35.0)	11 (3.3)	104 (31.1)	48 (14.4)	54 (16.2)
66-75	225	131 (58.2)	10 (4.4)	59 (26.2)	10 (4.4)	15 (6.7)
>75	332	245 (73.8)	4 (1.2)	54 (16.3)	6 (1.8)	23 (6.9)

Comorbidities	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
Yes	789	457 (57.9)	19 (2.4)	179 (22.7)	51 (6.5)	83 (10.5)
No	516	137 (26.6)	19 (3.7)	119 (23.1)	111 (21.5)	130 (25.2)

Source of admission	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
Same hospital	1069	473 (44.2)	29 (2.7)	243 (22.7)	146 (13.7)	178 (16.7)
Other hospital	233	120 (51.5)	9 (3.9)	55 (23.6)	16 (6.9)	33 (14.2)
Long-term chronic care hospital	2	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
Directly from the community	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)

Type of traumatic brain injury	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
Penetrating	51	37 (72.5)	0 (0.0)	7 (13.7)	1 (2.0)	6 (11.8)
Closed	1240	549 (44.3)	38 (3.1)	287 (23.1)	161 (13.0)	205 (16.5)
Unknown	13	7 (53.8)	0 (0.0)	4 (30.8)	0 (0.0)	2 (15.4)

Worst GCS (first 24 hours)	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
3-8	524	313 (59.7)	25 (4.8)	94 (17.9)	49 (9.4)	43 (8.2)
9-13	168	43 (25.6)	2 (1.2)	52 (31.0)	24 (14.3)	47 (28.0)
14-15	112	14 (12.5)	0 (0.0)	28 (25.0)	20 (17.9)	50 (44.6)
Not evaluable	501	224 (44.7)	11 (2.2)	124 (24.8)	69 (13.8)	73 (14.6)

Worst GCS during first 24h: best motor response	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
Obeys commands (6)	186	27 (14.5)	0 (0.0)	58 (31.2)	30 (16.1)	71 (38.2)
Localizes pain (5)	234	68 (29.1)	6 (2.6)	64 (27.4)	43 (18.4)	53 (22.6)
Withdraws to pain (4)	116	53 (45.7)	5 (4.3)	27 (23.3)	17 (14.7)	14 (12.1)
Flexion (abnormal) to pain (3)	55	36 (65.5)	0 (0.0)	11 (20.0)	5 (9.1)	3 (5.5)
Extension to pain (2)	73	49 (67.1)	4 (5.5)	15 (20.5)	3 (4.1)	2 (2.7)
None(1)	260	196 (75.4)	13 (5.0)	28 (10.8)	10 (3.8)	13 (5.0)
Not available	381	165 (43.3)	10 (2.6)	95 (24.9)	54 (14.2)	57 (15.0)

GCS trend in 48h	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
GCS 3 stable	97	78 (80.4)	7 (7.2)	8 (8.2)	3 (3.1)	1 (1.0)
GCS from 3 to 4-8	27	17 (63.0)	2 (7.4)	8 (29.6)	0 (0.0)	0 (0.0)
GCS from 3 to > 8	14	3 (21.4)	0 (0.0)	2 (14.3)	1 (7.1)	8 (57.1)
GCS from 4-8 to 3	50	40 (80.0)	4 (8.0)	4 (8.0)	1 (2.0)	1 (2.0)
GCS 4-8 stable	128	61 (47.7)	6 (4.7)	32 (25.0)	20 (15.6)	9 (7.0)
GCS from 4-8 to > 8	83	17 (20.5)	0 (0.0)	26 (31.3)	17 (20.5)	23 (27.7)
GCS from > 8 to 3	46	39 (84.8)	1 (2.2)	3 (6.5)	2 (4.3)	1 (2.2)
GCS from > 8 to 4-8	102	58 (56.9)	4 (3.9)	21 (20.6)	9 (8.8)	10 (9.8)
GCS > 8 stable	327	73 (22.3)	3 (0.9)	86 (26.3)	56 (17.1)	109 (33.3)

Clinically relevant hypotension	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
No	983	399 (40.6)	28 (2.8)	239 (24.3)	131 (13.3)	186 (18.9)
Yes	207	126 (60.9)	5 (2.4)	37 (17.9)	24 (11.6)	15 (7.2)
Not available	114	68 (59.6)	5 (4.4)	22 (19.3)	7 (6.1)	12 (10.5)

Clinically relevant hypoxia	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
No	886	368 (41.5)	20 (2.3)	218 (24.6)	120 (13.5)	160 (18.1)
Yes	303	151 (49.8)	12 (4.0)	61 (20.1)	37 (12.2)	42 (13.9)
Not available	115	74 (64.3)	6 (5.2)	19 (16.5)	5 (4.3)	11 (9.6)

Pupils in the emergency room	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
Bilaterally reactive and/or miotic	729	260 (35.7)	17 (2.3)	193 (26.5)	114 (15.6)	145 (19.9)
Unilaterally dilated and non-reactive	235	148 (63.0)	9 (3.8)	45 (19.1)	15 (6.4)	18 (7.7)
Bilaterally dilated and non-reactive	110	96 (87.3)	7 (6.4)	3 (2.7)	3 (2.7)	1 (0.9)
Not assessable	17	7 (41.2)	1 (5.9)	2 (11.8)	6 (35.3)	1 (5.9)
Not available	23	13 (56.5)	0 (0.0)	9 (39.1)	0 (0.0)	1 (4.3)

Anatomical severity (worst CT within 48 hours of admission)	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
Diffuse Injury I (no visible pathology)	131	34 (26.0)	2 (1.5)	28 (21.4)	24 (18.3)	43 (32.8)
(D-II) Diffuse injury II	413	87 (21.1)	10 (2.4)	124 (30.0)	85 (20.6)	107 (25.9)
Diffuse Injury III (edema)	136	68 (50.0)	3 (2.2)	34 (25.0)	16 (11.8)	15 (11.0)
Diffuse Injury IV (shift>5mm)	53	39 (73.6)	1 (1.9)	6 (11.3)	3 (5.7)	4 (7.5)
(5-EML) Evacuated mass lesion	420	248 (59.0)	19 (4.5)	86 (20.5)	28 (6.7)	39 (9.3)
(6-NEML) Not Evacuated mass lesion	151	117 (77.5)	3 (2.0)	20 (13.2)	6 (4.0)	5 (3.3)

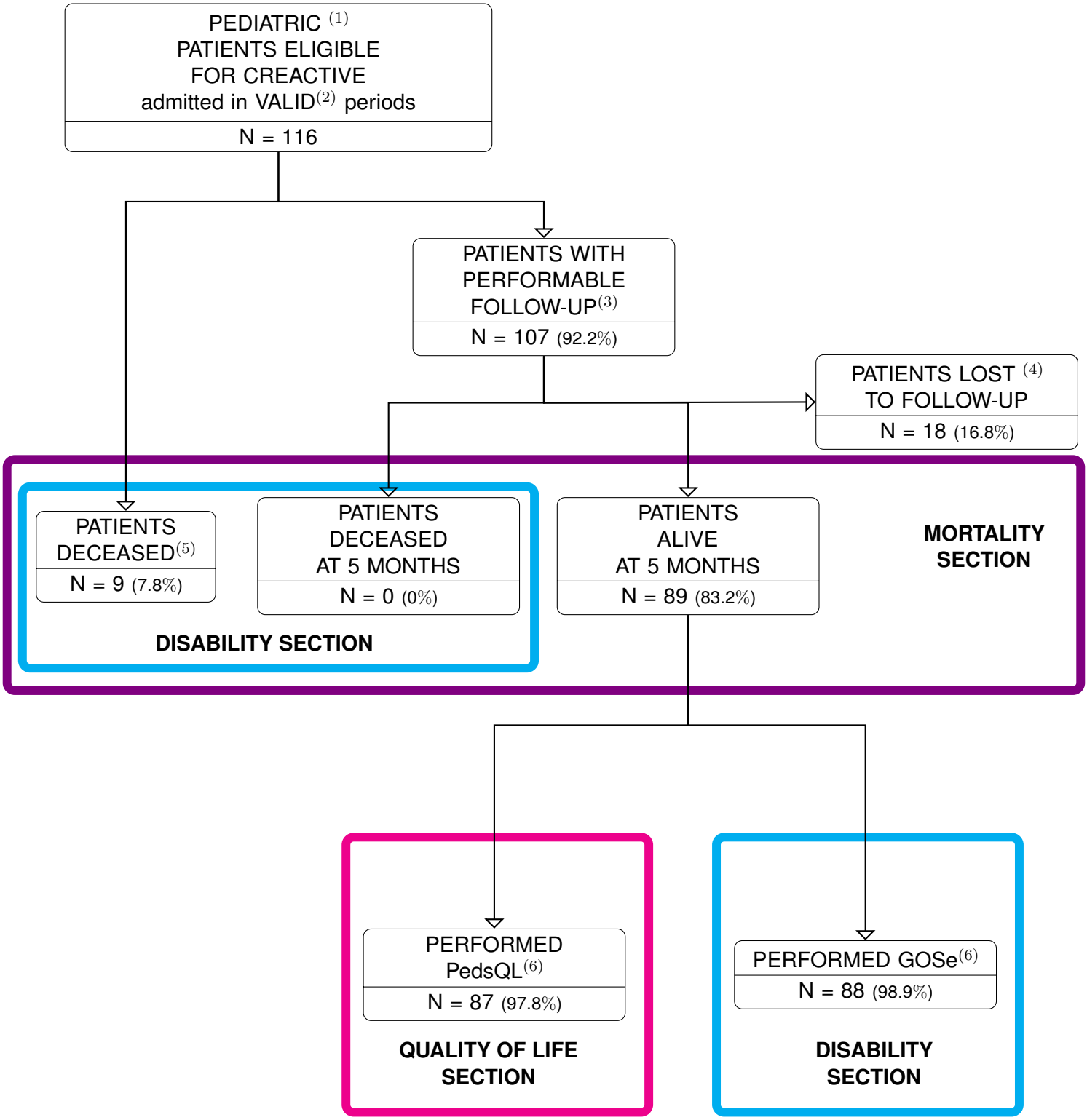
Patients (N): 227

QOLIBRI-OS score:	
Mean	72.8
SD	20.1
Median	75
Q1−Q3	62.5−87.5
Min−Max	0−100

			QOLIBRI-OS score:			
Anatomical severity (worst CT within 48 hours of admission) (N=227)	N	%	Mean	SD	Median	Q1-Q3
Diffuse Injury I (no visible pathology)	40	17.6	73.4	18.8	75.0	65.7−87.5
(D-II) Diffuse injury II	113	49.8	70.8	20.9	75.0	58.3−83.3
Diffuse Injury III (edema)	15	6.6	77.5	13.9	79.2	75−85.4
Diffuse Injury IV (shift>5mm)	6	2.6	82.6	17.8	89.6	68.8−94.8
(5-EML) Evacuated mass lesion	48	21.1	72.0	20.8	75.0	54.2−88.5
(6-NEML) Not Evacuated mass lesion	5	2.2	95.0	5.4	95.8	91.7−100

			QOLIBRI-OS score:			
GOSe result (N=223)	N	%	Mean	SD	Median	Q1-Q3
Deceased	0	0.0	-	-	-	-
Vegetative state	0	0.0	-	-	-	-
Severe disability	52	23.3	58.1	16.9	58.3	49−71.8
Moderate disability	72	32.3	70.1	17.9	70.8	62.5−80.2
Good recovery	99	44.4	83.4	16.8	87.5	75−95.8

Overall population with valid data (20 ICUs) - **Year 2017**
Follow-up flow-chart - Pediatric patients



(1) Patients under 17 years of age are considered PEDIATRIC patients.
(2) Periods are considered VALID when the % of complete data for core and petal are over the thresholds.
(3) Patients discharged alive > 5 months from the date of admission.
(4) This also includes patients declining to take part in the follow-up study or who are not contactable.
(5) Patients deceased in ICU or in hospital.
(6) Statistics are presented only for categories of patients represented by at least 5 subjects.

N.B. The % refers to the upper node in the flow chart.

Patients (N): 98

This section presents the mortality-related statistics.
Each of the tables provided is divided into two parts:

- the **first part** of each table (on the left-hand side, printed in black ink) refers to the ICU and the hospital mortality rates for each patient category.
  For example, 7.9% of the 63 patients aged between 9 and 16 years died in the ICU, while 7.9% died in hospital; 0% of the 13 patients aged between 2 and 4 years died in the ICU, while 0% died in hospital.
  This part of the table refers to all **pediatric CREACTIVE patients with valid data**.

- the **second part** of each table (on the right-hand side, printed in purple ink) refers instead to **pediatric CREACTIVE patients with valid data on whom we have 5-month outcome data** (alive or dead). The mortality rate at different time points (irrespective of the place of death - ICU, hospital, home) is shown for these patients: *within 4 days of the trauma event, between 4 and 7 days, between 8 and 30 days, and over 30 days*.
  For example, 55 of the valid pediatric CREACTIVE patients are aged between 9 and 16 years: of these, 5.6% died within 4 days of the trauma event, while the remaining 94.4% were still alive at that date. Accordingly, the only patients at risk of dying between 4 and 7 days are the ones still alive at day 4 *(55*0.944=52)*: 3.9% of these 52 died between 4 and 7 days. At this point, the only patients at risk of dying between 8 and 30 days are the ones who are still alive at day 8 *(i.e., 52*0.961=50)*; 0% of these died within 30 days.
  Hence, the sum of the percentages in each row does not produce 100%, since the denominator on which the rate is calculated varies for each column. To be precise, it consists of the number of subjects who are still alive at the start of the observation period of each column.

	All patients (N=116)			Patients with follow-up (N=98)				
Age	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
Newborn (0-4 weeks)	0	-	-	0	-	-	-	-
1-6 months	0	-	-	0	-	-	-	-
6-12 months	6	16.7	16.7	4	25.0	0.0	0.0	0.0
12-24 months	7	14.3	14.3	5	20.0	0.0	0.0	0.0
2-4 years	13	0.0	0.0	12	0.0	0.0	0.0	0.0
5-8 years	27	7.4	7.4	22	0.0	0.0	9.1	0.0
9-16 years	63	7.9	7.9	55	5.6	3.9	0.0	0.0

	All patients (N=116)			Patients with follow-up (N=98)				
Comorbidities	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
Yes	3	0.0	0.0	3	0.0	0.0	0.0	0.0
No	113	8.0	8.0	95	5.3	2.2	2.3	0.0

	All patients (N=116)			Patients with follow-up (N=98)				
Source of admission	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
Same hospital	82	8.5	8.5	69	5.9	1.6	3.2	0.0
Other hospital	29	6.9	6.9	26	3.8	4.0	0.0	0.0
Long-term chronic care hospital	0	-	-	0	-	-	-	-
Directly from the community	5	0.0	0.0	3	0.0	0.0	0.0	0.0

† Mortality (%)
* from TBI

	All patients (N=116)			Patients with follow-up (N=98)				
Type of traumatic brain injury	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
Penetrating	4	50.0	50.0	4	0.0	0.0	50.0	0.0
Closed	110	6.4	6.4	92	5.5	2.3	0.0	0.0
Unknown	2	0.0	0.0	2	0.0	0.0	0.0	0.0

	All patients (N=116)			Patients with follow-up (N=98)				
GCS worst (first 24 hours)	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
3-8	31	16.1	16.1	24	16.7	5.0	0.0	0.0
9-13	28	0.0	0.0	21	0.0	0.0	0.0	0.0
14	34	0.0	0.0	30	0.0	0.0	0.0	0.0
Not evaluable	23	17.4	17.4	23	4.3	4.5	9.5	0.0

	All patients (N=116)			Patients with follow-up (N=98)				
Worst GCS during first 24h: best motor response	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
Obeys commands (5)	51	0.0	0.0	41	0.0	0.0	0.0	0.0
Localizes pain (4)	27	0.0	0.0	23	0.0	0.0	0.0	0.0
Flexion to pain (3)	9	11.1	11.1	5	0.0	20.0	0.0	0.0
Extension to pain (2)	1	0.0	0.0	1	0.0	0.0	0.0	0.0
None(1)	5	80.0	80.0	5	80.0	0.0	0.0	0.0
Not available	23	17.4	17.4	23	4.3	4.5	9.5	0.0

	All patients (N=116)			Patients with follow-up (N=98)				
GCS trend in 48h	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
GCS 3 stable	4	100.0	100.0	4	100.0	-	-	-
GCS from 3 to 4-8	1	0.0	0.0	1	0.0	0.0	0.0	0.0
GCS from 3 to > 8	0	-	-	0	-	-	-	-
GCS from 4-8 to 3	0	-	-	0	-	-	-	-
GCS 4-8 stable	7	0.0	0.0	5	0.0	0.0	0.0	0.0
GCS from 4-8 to > 8	13	0.0	0.0	12	0.0	0.0	0.0	0.0
GCS from > 8 to 3	0	-	-	0	-	-	-	-
GCS from > 8 to 4-8	6	16.7	16.7	3	0.0	33.3	0.0	0.0
GCS > 8 stable	60	0.0	0.0	49	0.0	0.0	0.0	0.0

† Mortality (%)
* from TBI

General report - Year 2017
Follow-Up - 'Mortality' section: Mortality for main subgroups of patients - Pediatric patients

	All patients (N=116)			Patients with follow-up (N=98)				
Clinically relevant hypotension	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
No	80	1.2	1.2	65	0.0	1.5	0.0	0.0
Yes	16	31.2	31.2	15	33.3	0.0	0.0	0.0
Not available	20	15.0	15.0	18	0.0	5.9	12.5	0.0

	All patients (N=116)			Patients with follow-up (N=98)				
Clinically relevant hypoxia	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
No	66	4.5	4.5	55	3.6	1.9	0.0	0.0
Yes	33	9.1	9.1	29	10.3	0.0	0.0	0.0
Not available	17	17.6	17.6	14	0.0	7.7	16.7	0.0

	All patients (N=116)			Patients with follow-up (N=98)				
Pupils in the emergency room	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
Bilaterally reactive and/or miotic	69	0.0	0.0	57	0.0	0.0	0.0	0.0
Unilaterally dilated and non-reactive	6	0.0	0.0	4	0.0	0.0	0.0	0.0
Bilaterally dilated and non-reactive	6	83.3	83.3	6	83.3	0.0	0.0	0.0
Not assessable	0	-	-	0	-	-	-	-
Not available	3	0.0	0.0	3	0.0	0.0	0.0	0.0

	All patients (N=116)			Patients with follow-up (N=98)				
Anatomical severity (worst CT within 48 hours of admission)	**N**	**† in ICU(%)**	**† in H(%)**	**N**	**† within 4 days(%)***	**† 4-7 days(%)***	**† 8-30 days(%)***	**† over 30 days(%)***
Diffuse Injury I (no visible pathology)	21	0.0	0.0	16	0.0	0.0	0.0	0.0
(D-II) Diffuse injury II	46	0.0	0.0	39	0.0	0.0	0.0	0.0
Diffuse Injury III (edema)	13	30.8	30.8	12	18.2	11.1	12.5	0.0
Diffuse Injury IV (shift>5mm)	9	22.2	22.2	8	12.5	0.0	14.3	0.0
(5-EML) Evacuated mass lesion	27	11.1	11.1	23	8.7	4.8	0.0	0.0
(6-NEML) Not Evacuated mass lesion	0	-	-	0	-	-	-	-

† Mortality (%)
* from TBI

General report - Year 2017
Follow-Up - 'Disability' section - Pediatric patients

Patients (N): 97

GOSe result :*	All patients (N=97)		Alive patients (N=88)	
	N	%	N	%
Deceased	9	9.3	-	-
VEGETATIVE STATE	2	2.1	2	2.3
Severe disability LOWER LEVEL	6	6.2	6	6.8
Severe disability UPPER LEVEL	8	8.2	8	9.1
Moderate disability LOWER LEVEL	7	7.2	7	8
Moderate disability UPPER LEVEL	13	13.4	13	14.8
Good recovery LOWER LEVEL	16	16.5	16	18.2
Good recovery UPPER LEVEL	36	37.1	36	40.9

* patients with 'Pre-trauma disability' are not analyzed.

Disability for main subgroups of patients - N (%)

Age	N	Deceased	Vegetative state(%)	Severe disability(%)	Moderate disability(%)	Good recovery(%)
Newborn (0-4 weeks)	0	-	-	-	-	-
1-6 months	0	-	-	-	-	-
6-12 months	4	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (75.0)
12-24 months	4	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (75.0)
2-4 years	12	0 (0.0)	0 (0.0)	4 (33.3)	2 (16.7)	6 (50.0)
5-8 years	22	2 (9.1)	0 (0.0)	0 (0.0)	3 (13.6)	17 (77.3)
9-16 years	55	5 (9.1)	2 (3.6)	10 (18.2)	15 (27.3)	23 (41.8)

Comorbidities	N	Deceased	Vegetative state(%)	Severe disability(%)	Moderate disability(%)	Good recovery(%)
Yes	3	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	1 (33.3)
No	94	9 (9.6)	2 (2.1)	13 (13.8)	19 (20.2)	51 (54.3)

Source of admission	N	Deceased	Vegetative state(%)	Severe disability(%)	Moderate disability(%)	Good recovery(%)
Same hospital	68	7 (10.3)	2 (2.9)	10 (14.7)	17 (25.0)	32 (47.1)
Other hospital	26	2 (7.7)	0 (0.0)	3 (11.5)	3 (11.5)	18 (69.2)
Long-term chronic care hospital	0	-	-	-	-	-
Directly from the community	3	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (66.7)

Type of traumatic brain injury	N	Deceased	Vegetative state(%)	Severe disability(%)	Moderate disability(%)	Good recovery(%)
Penetrating	4	2 (50.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)
Closed	91	7 (7.7)	1 (1.1)	14 (15.4)	18 (19.8)	51 (56.0)
Unknown	2	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)

GCS worst (first 24 hours)	N	Deceased	Vegetative state(%)	Severe disability(%)	Moderate disability(%)	Good recovery(%)
3-8	23	5 (21.7)	0 (0.0)	7 (30.4)	3 (13.0)	8 (34.8)
9-13	21	0 (0.0)	0 (0.0)	4 (19.0)	3 (14.3)	14 (66.7)
14	30	0 (0.0)	0 (0.0)	1 (3.3)	9 (30.0)	20 (66.7)
Not evaluable	23	4 (17.4)	2 (8.7)	2 (8.7)	5 (21.7)	10 (43.5)

Worst GCS during first 24h: best motor response	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
Obeys commands (5)	41	0 (0.0)	0 (0.0)	4 (9.8)	10 (24.4)	27 (65.9)
Localizes pain (4)	22	0 (0.0)	0 (0.0)	6 (27.3)	3 (13.6)	13 (59.1)
Flexion to pain (3)	5	1 (20.0)	0 (0.0)	2 (40.0)	1 (20.0)	1 (20.0)
Extension to pain (2)	1	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
None(1)	5	4 (80.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)
Not available	23	4 (17.4)	2 (8.7)	2 (8.7)	5 (21.7)	10 (43.5)

GCS trend in 48h	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
GCS 3 stable	4	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GCS from 3 to 4-8	1	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
GCS from 3 to > 8	0	-	-	-	-	-
GCS from 4-8 to 3	0	-	-	-	-	-
GCS 4-8 stable	4	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	3 (75.0)
GCS from 4-8 to > 8	12	0 (0.0)	0 (0.0)	4 (33.3)	3 (25.0)	5 (41.7)
GCS from > 8 to 3	0	-	-	-	-	-
GCS from > 8 to 4-8	3	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)
GCS > 8 stable	49	0 (0.0)	0 (0.0)	5 (10.2)	11 (22.4)	33 (67.3)

Clinically relevant hypotension	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
No	64	1 (1.6)	1 (1.6)	10 (15.6)	12 (18.8)	40 (62.5)
Yes	15	5 (33.3)	0 (0.0)	2 (13.3)	4 (26.7)	4 (26.7)
Not available	18	3 (16.7)	1 (5.6)	2 (11.1)	4 (22.2)	8 (44.4)

Clinically relevant hypoxia	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
No	54	3 (5.6)	1 (1.9)	9 (16.7)	10 (18.5)	31 (57.4)
Yes	29	3 (10.3)	0 (0.0)	3 (10.3)	8 (27.6)	15 (51.7)
Not available	14	3 (21.4)	1 (7.1)	2 (14.3)	2 (14.3)	6 (42.9)

Pupils in the emergency room	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
Bilaterally reactive and/or miotic	56	0 (0.0)	0 (0.0)	10 (17.9)	13 (23.2)	33 (58.9)
Unilaterally dilated and non-reactive	4	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	2 (50.0)
Bilaterally dilated and non-reactive	6	5 (83.3)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Not assessable	0	-	-	-	-	-
Not available	3	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (66.7)

Anatomical severity (worst CT within 48 hours of admission)	N	**Deceased**	**Vegetative state(%)**	**Severe disability(%)**	**Moderate disability(%)**	**Good recovery(%)**
Diffuse Injury I (no visible pathology)	16	0 (0.0)	0 (0.0)	3 (18.8)	5 (31.2)	8 (50.0)
(D-II) Diffuse injury II	38	0 (0.0)	1 (2.6)	5 (13.2)	8 (21.1)	24 (63.2)
Diffuse Injury III (edema)	12	4 (33.3)	1 (8.3)	1 (8.3)	4 (33.3)	2 (16.7)
Diffuse Injury IV (shift>5mm)	8	2 (25.0)	0 (0.0)	1 (12.5)	0 (0.0)	5 (62.5)
(5-EML) Evacuated mass lesion	23	3 (13.0)	0 (0.0)	4 (17.4)	3 (13.0)	13 (56.5)
(6-NEML) Not Evacuated mass lesion	0	-	-	-	-	-

Patients (N): 87

PedsQL - TOTAL SCORE	
Mean	75.1
SD	24.5
Median	83
Q1−Q3	59−97
Min−Max	0−100

			PedsQL - TOTAL SCORE			
Anatomical severity (worst CT within 48 hours of admission) (N=87)	N	%	Mean	SD	Median	Q1-Q3
Diffuse Injury I (no visible pathology)	15	17.2	77.2	16.2	76.0	68−90.5
(D-II) Diffuse injury II	38	43.7	77.3	24.5	84.5	61.2−97.8
Diffuse Injury III (edema)	8	9.2	55.4	28.5	58.5	45−74.8
Diffuse Injury IV (shift>5mm)	6	6.9	90.5	13.7	94.5	90.2−99.5
(5-EML) Evacuated mass lesion	20	23.0	72.4	27.3	84.0	53−94
(6-NEML) Not Evacuated mass lesion	0	0.0	-	-	-	-

			PedsQL - TOTAL SCORE			
GOSe result (N=87)	N	%	Mean	SD	Median	Q1-Q3
Deceased	0	0.0	-	-	-	-
Vegetative state	2	2.3	0.0	0.0	0.0	0−0
Severe disability	14	16.1	49.4	18.8	50.5	38.8−62.5
Moderate disability	20	23.0	64.6	15.4	65.5	51−73.8
Good recovery	51	58.6	89.1	14.0	94.0	85−98

creactive

You are warmly invited to the

CREACTIVE Satellite Symposium

Can we improve prognostication in TBI?

Preliminary results from CREACTIVE.

Moderator: ***Isaac Lazar*** *(Israel)*

Thursday, 21 March, 2019
Silver Hall (18:15 - 19:45)

18:15 - 18:25 **The CREACTIVE study on moderate-to-severe TBI patients admitted to the ICU: advancing outcome prediction**
Speaker: ***Guido Bertolini*** *(Italy)*

18:25 - 18:45 **Biofluid biomarkers in TBI: towards a bedside prognostic tool**
Speaker: ***Primoz Gradisek*** *(Slovenia)*

18:45 - 19:00 **Discussant**
David J Sharp *(UK)*

19:00 - 19:05 **Question time**

19:05 - 19:25 **Imaging biomarkers in TBI: machine learning applied to TBI imaging**
Speaker: ***Luca Antiga*** *(Italy)*

19:25 - 19:40 **Discussant**
David K Menon *(UK)*

19:40 - 19:45 **Question time**

The research leading to these results has received funding from the European Commission Seventh Framework programme (FP7/2007-2013), under grant agreement no. 602714 (CREACTIVE)

GiViTI

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InTBIR Data Sharing Principles Document

Background

The InTBIR Initiative, hereinafter referred to as InTBIR, is a cooperative effort of the European Commission (EC), the National Institutes of Health (NIH), the US Department of Defense (DoD), the Ontario Brain institute (OBI) and OneMind that aims to coordinate and leverage international clinical research activities on traumatic brain injury (TBI) research.

The long-term goal of InTBIR is to improve outcomes and lessen the global burden of TBI by 2020 by supporting well-designed, hypothesis-driven studies collecting high quality data followed by rigorous statistical analysis. By taking advantage of widespread variability in how patients are treated, InTBIR aims to identify causal relationships associated with clinically meaningful outcomes.

One of the key aims of InTBIR is to promote the ethical sharing of data across the TBI research field and to facilitate collaboration. Accordingly, the calls for proposals under the InTBIR Initiative included a mandate for the collection of Common Data Elements (CDEs) and the establishment of databases to permit data sharing with other members of the InTBIR consortium. The requirement that, as of July 2018, all manuscripts submitted to International Committee of Medical Journal Editors (ICMJE) journals must contain a data sharing statement further highlights the importance of openness to collaborative research.

InTBIR has a duty to create a data sharing environment that is secure for the patients, that protects ownership, that allows for maximum use of data collected via studies funded by taxpayers, and that clearly assign authorship credit.

Objectives

The aim of InTBIR is to promote the use of consistent defined standards within a CDE approach and to develop and implement a federated system for maximizing the use of patient-level information on clinical, phenotypic, genomic and imaging features.

The InTBIR Data Sharing Principles are intended to serve as a guide to collection, standardization, and sharing of clinical TBI data for comparative effectiveness research, ultimately resulting in better management and treatments for TBI. They strive to align with the ***FAIR Guiding Principles for scientific data management and stewardship***, which were developed to provide guidelines to improve the findability, accessibility, interoperability, and reuse of data.

The principles included in this document are subject to revisions by the InTBIR Leadership. They should not be considered static but are expected to evolve over the course of time. Specifics of operationalizing the InTBIR Data Sharing principles are not included within the scope of this document.

Data Sharing

Data Sharing Environment

InTBIR studies should strive to use Common Data Elements and standardized protocols to encourage consistency across datasets and familiarity with data elements and study procedures. InTBIR studies should securely store data within geographical regions or jurisdictions, and have compatible data for federation within and across geographical regions or jurisdictions.

Data Quality

To ensure the quality of data made available via InTBIR, data made available to the data centers should:

- Comprise research/clinical assessments/information obtained via interviews, direct observations, laboratory tasks and procedures, record reviews, genetic and genomic data, neuroimaging data, neuropsychological assessments, data from physical examinations, etc., but must EXCLUDE demographic data that could permit easy re-identification of individual patients;
- Include supporting documentation that aims to make data accessible, understandable and usable by investigators unfamiliar with the dataset. Supporting documentation may, for example, include non-copyrighted data collection forms, study procedures and protocols (including patient consent documents), data dictionary rationale, exclusion criteria, website references, a listing of major study publications, and the definition of genomic analysis protocols;
- Be collected in a manner consistent with institutional policies, and local/national regulations and policies;
- Be collected using the International TBI Common Data Elements to the greatest extent possible https://intbir.nih.gov/icdes
- Be encoded using data formats that are consistent with commonly used standards;
- When available, feasible, and appropriate to study goals, follow standardized protocols for collection, storage, and transfer of biospecimens, imaging, genomics, and other research methods.
- Have quality assurance algorithms linked to the data sets whenever possible to ensure data formats and consistency.

Patient security (*also see informed consent principles*)

The identity of research subjects must be protected. Each individual data center will adhere to national law and the respective legal requirements for data sharing in the country in which it is based.

Investigators providing data to any established data center should assure that:

- All data provided to the data center are consistent with all applicable laws, regulations, and institutional policies;
- The data have been encoded at the source using an identifier which is unique to each individual research participant (use of a Global Unique Identifier (GUID) as adopted in the US based Federal Interagency Traumatic Brain Injury Research (FITBIR) database, which enables data to be associated with a participant without exposing or transferring Protected Health Information (PHI), is strongly recommended);
- Algorithms that satisfactorily purge medical data sets of possible identifiers are used in the de-identification process whenever possible.

An Institutional Review Board (IRB) and/or the Data Protection Officer/Privacy Board (as applicable) of the entity providing data should determine that:

- The data made available for sharing for research purposes are consistent with the informed consent obtained from the research subjects from whom the study data was obtained.
- The data made available have been appropriately de-identified/anonymized (consistent with current standards and respective applicable legislative provisions) to ensure its use in a secure environment.
- Risks to individuals, their families, and groups or populations associated with the data have been minimized.
- Data should be used appropriately and only as far as explicitly allowed for by the respective informed consent documents.
- If consent documents stipulate restrictions concerning the use/re-use of the respective data, these should be prominently displayed in the data sets provided.

Protecting ownership (*see Publication Principles*)

At a minimum, all researchers who access InTBIR data are expected to acknowledge in all resulting presentations, disclosures, or publications of the analyses:

- The funding organization(s) that supported their work;
- The Contributing Investigator(s) who conducted the original study;
- The InTBIR initiative as such

Data usage and quality control

Clinical data collected should use widely accepted common data elements/data acquisition protocols and conform to the highest possible standards so it can be used by the widest possible array of users, whether academic, medical, clinical, or commercial.

Researchers should make data available to the research community as soon as possible after study completion. Access to data should be subject to relevant data use agreements and should be made available via a standard application process to ensure appropriate use of the data.

Consistent with protecting patient privacy, informed consents for collection of medical data obtained from patients should permit use of their de-identified (anonymous) data for research in as wide a range as possible. (*See Informed Consent Principles*)

Data access privileges

Data access privileges should be safeguarded by Data Centers and their specific policies. Overarching principles applicable to InTBIR data include:

- Data should be made accessible only for approved research as per the Informed Consent given following appropriate data security procedures;
- Compliance with applicable laws, regulations and local institutional policies and data handling procedures;
- Keeping the data obtained from InTBIR datasets confidential from non-authorized third parties;

- Adherence to the InTBIR Data Sharing Principles, including its provisions on publication of research results emanating from InTBIR data sets;
- Making data accessible at varying levels and giving permissions accordingly;
- Providing only descriptive summary information of accessible data for use by the general public;
- Data should be made accessible as permitted by secondary data use restrictions;
- Data accessibility will depend both on the embargo periods of the partner projects and on national regulations regarding the across jurisdiction transfer of clinical data;
- Access to data or certain components of the data will be restricted to qualified researchers who comply with all applicable rules, laws, regulations or policies (e.g., IRBs, human subjects, informed consent, etc.).

Informed Consent Principles

General principles

The InTBIR Informed Consent Principles recommend streamlined and standardised informed consent wording and content, with the intent to enable and reinforce data sharing across InTBIR studies, *including providing for explicit permission for cross-jurisdiction data transfer*. Wording should be based on an adaptation or extension of what has been used by the original InTBIR studies, thus minimising the need to go back to subjects for further consent.

The Principles aim to balance two important objectives: to facilitate data sharing and to respect and protect the participants who have contributed their personal data and materials to InTBIR. Accordingly, participants need to be informed that their data will be de-identified such that there is a low risk that identities of data subjects could be ascertained or otherwise associated with the respective data under study, either by InTBIR study staff or secondary data users (if for the latter consent has been given). The information sheet must also explicitly state that sufficient data encryption and protection standards are in place to guarantee that patient data will only be shared in a secure network.

Publication Principles

The overall aim of the Publication Principles is to stimulate and streamline high-quality scientific output produced jointly by members of InTBIR.

General principles

- For the purposes of this policy, the term “publication” refers to manuscripts in scientific journals.
- These principles refer to publications including data from at least two InTBIR studies or on topics of general principles and policies relating to InTBIR.
- InTBIR is strongly in favor of promoting extensive dissemination of InTBIR data and of data sharing.
- Publications across studies are strongly encouraged but should not jeopardize primary publications from individual InTBIR studies. Open Access publications are preferred.

Specific goals

- Maximize and accelerate scientific output;
- Increase efficiency and avoid duplication for research;
- Define authorship criteria, fostering the participation of several different InTBIR study investigators (multistudy authorship) in the production of valuable scientific outputs;
- Maintain transparency towards InTBIR collaborators, and external data requests;
- Promote visibility of InTBIR

All study plans/titles should be listed on the InTBIR website (title, aim, PI), so as to be accessible to the InTBIR research community.

Principles for publications emanating from InTBIR studies

Publications based on data generated under two or more of the participating InTBIR studies shall undertake to ensure:

- methodological soundness;
- correct use of and scientifically appropriate interpretation of the data;
- adherence to criteria for authorship;
- inclusion of appropriate acknowledgements.

Authorship, denoted as those on the first line(s) of the authorship attribution in a journal and in indexing services, should be based on appropriate effort and comply with the following four guidelines published by the International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org/roles_a.html).

Primary authors should meet all four of the following criteria:

a. Substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; AND
b. Drafting or critical revision of the work for important intellectual content; AND
c. Final approval of the version to be published; AND
d. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The corresponding author shall be responsible for notifying the InTBIR Leadership of all accepted manuscripts, including the journal title, date of publication, page number(s) and other reference information for the publication/presentation. The InTBIR Leadership will make a record of all accepted abstracts, presentations and publications relating to InTBIR, which will be posted on the InTBIR website.

Authorship credit will be automatically granted to all InTBIR Participants and Investigators who fulfil all four above-mentioned criteria. All publications using InTBIR data shall state the following at the end of the author list: "*and the InTBIR Investigators*," to represent those investigators involved in the data acquisition, who will be listed as collaborators in alphabetical order. Contributors who meet fewer than all four of the above-mentioned criteria will not be listed as authors but should be acknowledged.

All publications shall acknowledge the *source(s) of the data* as derived from two or more InTBIR studies. Data analyzed by Investigators external to the InTBIR studies should also carry a disclaimer stating that the publication/communication reflects the interpretation only of the author(s). All publications should

make explicit reference to the *sources of funding* [European Commission/NIH/CIHR/DoD/xxx, Grant Agreement/Contract no. xxx].

Additional recommendations for all publications, including those emanating from single InTBIR studies

We strongly encourage all studies funded under the InTBIR umbrella to include InTBIR in the acknowledgements section of every manuscript. This applies also to publications by investigators from outside the InTBIR studies using InTBIR data sets or where InTBIR has otherwise contributed to bonification of study methods, or interpretation of data. The addition of InTBIR in the acknowledgement section would also serve to increase the visibility of InTBIR globally, as InTBIR-derived or –linked publications shall be listed on an InTBIR publications depository accessible through the InTBIR website.

The publications' metadata will be added to the relevant InTBIR databases, e.g. FITBIR, OBI-BrainCode and the Human Brain Project.