Protocol BRAINI2-IMPLEMENTATION STUDY

Registration No.: No.

Ref: TP25/0144

Blood Biomarkers to improve management of mild traumatic BRAIN Injury implementation study

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Fundación Investigación Biomédica Hospital 12 de Octubre (FIBH12O)

This work is supported by EIT-Health funding.

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1. STUDY SUMMARY

TITLE	Blood Biomarkers to improve management of mild traumatic BRAIN Injury implementation study
RUNNING TITTLE	BRAINI2 Implementation study
GENERAL OBJECTIVE	To assess the applicability and added value of a new clinical management pathway for patients with mild TBI presenting to the emergency department (ER), including the use of an in vitro diagnostic assay measuring the biomarkers GFAP and UCH-L1 in the serum, within the first 12 hours post-injury, to rule out the need for CT scan in mild TBI patients.
PRINCIPAL OBJECTIVE	1) To evaluate the diagnostic performance of the VIDAS TBI (GFAP&UCH-L1) test in determining the need for CT-scan in patients with mild TBI admitted to the ER of Hospital 12 de Octubre. 2) To determine the safety of a management protocol including the use of the VIDAS GFAP&UCH-L1 test for patients with mTBI, in terms of complications or unforeseen neurological deterioration following the injury. 3) To estimate the reduction of CTs achieved using the biomarker test, by comparison with the management of TBI during the six months preceding the study (reference pathway).
PRINCIPAL OUTCOME	Abnormal CT scan at admission in the ER Deterioration: need for hospital admission or surgery due to TBI in the first week after TBI Number of CTs prescribed in the management of mild TBI patients in the ER
PRINCIPAL OUTCOME MEASURES	1) Diagnostic performance of the biomarker test 2) Proportion (%) of neurologic deterioration within 1 week post-TBI 3)Proportion (%) of CT scan prescribed in the ER over the period of the study for patients with mTBI
SECONDARY OBJECTIVES	2.1) To determine the different times involved in the management of mild TBI patients and the effect of using the combined VIDAS test. 2.2) To establish differences in direct costs in the management of mild TBI in Hospital 12 de Octubre. 2.3.) To assess the compliance of physicians to the proposed algorithm.
SECONDARY OUTCOMES	2.1) Time from admission to discharge. Time from admission to sample obtention. Time from venipuncture to availability of biomarker results. 2.2) Directs costs associated with mTBI management in the ER. 2.3.) Compliance with proposed algorithm.
SECONDARY OUTCOME MEASURES	2.1) Time differences with respect to reference group 2.2) Cost difference comparing before and after the implantation of the biomarker test. 2.3) Proportion (%) of cases in which management follow the proposed algorithm

METHODOLOGY	The study will compare the different outcome measures between a historic group obtained 6 months before the initiation of the new management protocol and the group of patients admitted in the ER with a diagnosis of a mTBI after the initiation of the new bundle of care. The combined GFAP&UCH-L1 test has been included in the new bundle of care of mTBI for the management in the ER of all patients with mTBI. In summary the test will be performed to all patients with mTBI admitted to the ER of Hospital 12 de Octubre and included in the new management pathway of patients with mTBI incorporated in our hospital. All patients suffering a mTBI(GCS 15-13) and admitted within 12 hours of the TBI will be included in this pathway. If the patient is included in this pathway, the prescription of cranial CT will be performed following the results of the VIDAS TBI test if the patient has had a significant TBI and a GCS of 14 or 15. Those patients with GCS of 13 or a focal neurological deficit will receive both biomarkers and CT for their management during the study period. The VIDAS TBI test interpretation as defined by the manufacturer, bioMérieux, takes into account the responses of the two biomarkers: the VIDAS TBI test is negative if the two markers GFAP and UCH-L1 are negative (below the previously defined threshold concentration for each of the biomarkers). The test is positive if at least one of the two GFAP or UCH-L1 biomarkers is positive (beyond the threshold concentration). This test is already CE marked and has already been tested on a large number of European patients and has demonstrated good safety and reliability profiles.
STUDY TYPE	Protocol evaluation Implementation Study
STUDY DESIGN	Implementation study with prospective data collection with a control reference historic group
STUDY POPULATION	Mild TBI patients with significant brain trauma admitted in the ER of Hospital 12 de Octubre
INCLUSION CRITERIA	-All adult patients suffering mild TBI:(Defined by at least criterion a) and d) and one or more of the other criteria) a) The presence of a plausible traumatic mechanism observed/or related by the patient´s recount of the injury event. b) Presence of one or more clinical signs attributable to brain injury: Loss of consciousness immediately following injury, alteration of mental status immediately following the injury, posttraumatic amnesia or any neurological abnormality. c) At least two acute symptoms related to the injury: feeling confused or disoriented, headache, nausea, vomiting, dizziness, vision problems, memory problems, emotional lability or irritability. d) a GCS between 15 and 13, at least 30 minutes after injury. -Blood sample obtained ≤12 h after injury and ideally before any imaging prescription.
EXCLUSION CRITERIA	· GCS 3-12 on admission · Age Below 18 years · Time of injury unknown · Time to injury exceeding 12 hours

	· Primary admission for non-traumatic neurological disorder (e.g., stroke, spontaneous, intracranial hematoma) · Penetrating head trauma · Patient with mechanical ventilation from the trauma scene or prehospital management · Venipuncture not feasible
NUMBER OF SUBJECTS	The implementation study will last for 6 months. The number of patients that are normally treated for this pathology is around 3000 patients each year. During the 6 months of the study around 1000 patients will at least be triaged for mild TBI
STUDY CENTRES	Hospital 12 de Octubre
PROVISIONAL CALENDAR OF THE STUDY	- Start of inclusions: Jan 2025 - Inclusion period: 6 months - End of inclusions: July 2025 - Length of participation of each subject: 2 weeks - Total length of the study: 6 months
STATISTICAL ANALYSIS	Outcome assessment CT scan status will be attributed to each study participant based on the presence of intracranial lesions. Local CT reading will be used. Outcome assessors will be blind to the participant biomarker status. Quality control outcome assessment will be performed over the study period via sequential intra/inter observer agreement assessment.
EXPECTED IMPACT	This study will demonstrate the feasibility of using a bundle of care based on the determination of blood-based brain biomarkers in the management of patients with mTBI, in a real-life setting. It will also determine the time needed for obtaining results of these blood derived biomarkers and if there is reduction in associated cost and CT prescription related to its use.

2. RATIONALE FOR THE STUDY

2.1. Background and current management

Traumatic brain injury (TBI) is a major large public health and societal problem with an annual incidence of 262 per 100.000 patients in Europe. TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force. Clinical severity of TBI lies on a continuum graded by the Glasgow Coma Scale score from which TBI has been classified in the broad categories of "severe (GCS 3-8)", "moderate (9-12)", and "mild (13-15)". Research has focused for a long time in the more severe forms of TBI, due to its more evident catastrophic consequences to life. However, mild TBI is the more frequent form of TBI (70-80% of all TBI), and therefore pose the greatest health care burden caused by TBI [1,2]. The population affected by TBI depends on the degree of development of the country, and as the population ages, the number of patients affected by TBI increases, specifically in this form of mTBI. The most frequent cause of mTBI nowadays is falls and this incises in the aged group of European population.

The initial management of mild TBI in the ED relies on performing a non-contrast brain CT if the patient meets specific conditions. Efforts have been made to optimize the indications for Brain CT scan after mTBI such as different clinical decision rules (CDRs) such as the Canadian Head CT rule[3] or the New Orleans criteria[4]. However the prevalence of CT detected abnormalities is less than 10% in patients with mTBI and a minority of these patients with intracranial lesions will require a neurosurgical procedure (1%).

Several aspects are in controversy in the management of patients with mTBI. In the ER[5-8], the need for performing or not a CT, the value of the CDRs and protocols used in the ER to select those patients in need of having a CT performed and the value of serum biomarkers for selecting these patients in need of further examination has been thoroughly studied[9-18]. The variability in the management of mTBI between different hospitals within a country and in Europe (16)(and publication in press from our group) implies that CDRs are not correctly followed by physicians attending these patients due to the complexity of these rules, the difficulty in actually applying them in certain conditions such as intoxicated patients, hearing loss or speech difficulties, and the insecurity many physicians and patients have to being discharged without a CT. As a consequence, up to 40% of CT scans obtained in the ER would actually not follow these CDRs. Therefore, the number of CTs performed for this condition is very high, with important consequences for health expenditure and radiation exposure to patients. This is also a specific and important problem for elderly patients. Intracranial changes that occur with aging as well as the increasing prevalence of comorbidities and antithrombotic medication use put the elderly at an increased risk of intracranial bleeding after low velocity falls. Most CDRs use age over 60 or 65 as one of the factors associated with use of CT scan after mTBI. Elderly patients are therefore at an increased risk of CT overuse as they suffer many times from recurrent falls and sometimes receive one CT for each fall.

Patients with mTBI lesions are often hospitalised in the standard ward where neurological monitoring consists of repeated CT scanning and clinical exams. Patients without lesions on the initial head CT-scan are also hospitalised when their GCS score after CT scan is less than 15.

Additionally, elderly patients on anticoagulants or antithrombotic drugs are more frequently hospitalised due to physicians' concerns about potential deterioration. This determines a bigger number of unneeded hospitalisations for these patients.

Therefore, although CT scan plays a pivotal role in the management of mTBI, there is an unmet clinical need for an objective tool to optimize and guide indications for CT scan, reduce clinical practice variability, reduce patient radiation exposure and improve patient outcome prediction.

2.2. Blood Biomarkers in mTBI

Serum biomarkers have appeared as a possible solution for determining the need for CT in patients with mTBI. S-100B has been incorporated in one of the CDR (The Scandinavian mild head injury management guidelines)[17,18]. However, the use of this biomarker is restricted to Scandinavian countries and has not gained acceptance in any other country. There are specific concerns regarding its negative predictive value, the variation of its concentration regarding skin color or the increase in its concentration when there is systemic trauma[21,22]. GFAP and UCHL1 are two brain specific biomarkers that have recently been demonstrated to have in combination a very high negative predictive value for demonstrating lesions in CT and there is some data regarding their possible role in determining prognosis and even their ability to determine which patients could have lesions detectable in MRI[23].

Recently a new algorithm including blood biomarkers (GFAP and UCH-L1) has been proposed in the management of mTBI patients in Spain supported by different organizations and medical societies including the Spanish Neurosurgical Society. This algorithm has not yet been studied for its net benefit in reducing costs or the number of CTs prescribed. Additionally, there is no data on the time needed to provide accurate results available to the clinician. Nevertheless the recommended algorithm has been adopted and proposed by different medical societies, including the Spanish Society for emergency Medicine and the Spanish Society of Neurological Surgeons (SENEC). This algorithm will be adopted by the Department of Neurosurgery of this Hospital in order to implement this new solution.

2.3. VIDAS TBI

The VIDAS TBI assay is an automated, quantitative, enzyme-linked immunofluorescent assay (ELFA) for the detection of Ubiquitin C-terminal Hydrolase-L1 (UCH-L1) and Glial Fibrillary Acidic Protein (GFAP) in blood serum. The assay is to be used in conjunction with other clinical information, as an aid in the evaluation of adult patients with mTBI (with Glasgow Coma Scale score (15-13) within 12 hours of injury to assist in determining the need for a CT scan of the head. This assay has been assessed in the BRAINI study[24] and is now CE marked and FDA approved. There is no data regarding the practical use or real-world data including the use of the VIDAS GFAP&UCH-L1 assay.

3. STUDY OBJECTIVES AND OUTCOME MEASURES

3.1. GENERAL OBJECTIVE

The general objective of BRAINI-2-Implementation Study is to assess the performance of the biomarkers GFAP and UCH-L1 in real life and to assess their safety of use when incorporated into the clinical management of the patient and to establish their acceptance and integration into an already accepted management pathway.

3.2. PRIMARY OBJECTIVE AND OUTCOME MEASURE

The primary objective of the study is to evaluate the performance of the two biomarkers GFAP and UCH-L1 assay to rule out the need for CT scan after mTBI.

The primary outcome will be the result of brain CT. Performance of the test will be analysed, as described in the assay instruction for use, to rule out the need for a CT scan after mTBI.

CT results will be obtained following the usual management pathway, using local radiologist report to determine the presence of pathological findings. Patients in whom no CT will be performed (i.e.: some GCS 15 without RF and GCS 14 with negative biomarkers test), will be ascribed as CT negative for the analysis if there is no deterioration or further evaluation that determines the need for a CT for other reasons.

Both GFAP and UCH-L1 biomarkers will be tested by two separate immunological assays using the usual clinical management and pathway in the management of mTBI. The positivity thresholds for each of the biomarkers and the two biomarkers' combination were validated by the company Banyan Biomarkers in an independent study, ALERT-TBI [13] and confirmed by bioMérieux using the VIDAS TBI with the same ALERT-TBI cohort and with the BRAINI study. The test will be performed if the patient is included in the new management pathway of patients with mTBI incorporated in our hospital. If the patient is included in this pathway, the prescription of cranial CT will be performed following the results of the VIDAS TBI test obtained. Patients with GCS of 13 will receive both biomarkers and CT scan for their management. Patients not following the clinical pathway (GCS<13 or non TBI patients) will be excluded from the study and managed according to routine clinical practice.

The VIDAS TBI test interpretation as defined by the manufacturer, bioMerieux, takes into account the responses of the two biomarkers: the VIDAS TBI test is negative if the two markers GFAP and UCH-L1 are negative (below the previously defined threshold concentration for each of the biomarkers). The test is positive if at least one of the two GFAP or UCH-L1 biomarkers is

positive (beyond the threshold concentration). This test has been already tested in a large number of European patients and has presented good safety and reliability profiles.

To determine the safety of the new protocol all information regarding the neurological status of the patients in relation to mTBI will be analyzed up to two weeks after the mTBI, specifically neurological deterioration, need for further observation of the patient or admission or need for treatment(medical or surgical) related to mTBI.

In order to determine the reduction of CT scans obtained with this new protocol, absolute numbers and proportions of patients finally scanned using this new protocol will be compared to the reference management of a similar number of patients during a similar historical period(i.e. data from the previous six month for patients attended for mTBI at Hospital 12 de Octubre).

3.3. SECONDARY OBJECTIVES AND OUTCOME MEASURES

Different secondary objectives are planned in this study with corresponding outcome measures:

3.3.1. Time lapse needed in the management of mTBI in the ED:
a)From TBI to VIDAS TBI result.
b)From admission to VIDAS TBI result available for physician.
c)From TBI to CT and from admission to CT.
d)General management of TBI in the ER.
Outcome measures will be time to achieve each these steps in management, obtained directly from the Hospital´s information and data systems.

3.3.2. Direct costs consumption will be obtained from each ER episode of included patients and compared to age-matched historical controls (patients managed in Hospital 12 de Octubre for mTBI in the previous six months before implementation of the new protocol).

3.3.3. Assessment of the proportion of cases being managed following the proposed algorithm

4. STUDY DESIGN

4.1. STUDY OVERVIEW AND STUDY POPULATION

This is a single center study with prospective data collection with a control reference group.

Patients to be included in the new clinical pathway:

-Adult Patients (≥18 years of age) suffering mild TBI:(Defined by at least criterion a) and e) and one or more of the other criteria)

a) The presence of a plausible traumatic mechanism as described by the patient´s recount of the injury event.

b) Presence of one or more clinical signs attributable to brain injury: Loss of consciousness immediately following injury, alteration of mental status immediately following the injury, posttraumatic amnesia or any neurological abnormality.

c) At least two acute symptoms related to the injury: feeling confused or disoriented, headache, nausea, vomiting, dizziness, vision problems, memory problems, emotional lability or irritability.

e) GCS between 15 and 13, assessed at least 30 minutes after injury.

-Blood sample obtained ≤12 h after injury and before any imaging prescription.

Patients will not be included in the new pathway if:

· GCS 3-12 on admission

· Time of injury unknown

· Time to injury exceeding 12 hours

· Primary admission for non-traumatic neurological disorder (e.g., stroke, spontaneous, intracranial hematoma)

· Penetrating head trauma

· Patient with mechanical ventilation from the trauma scene or prehospital management.

· Venipuncture not feasible

Participation in the study will not affect patient management.

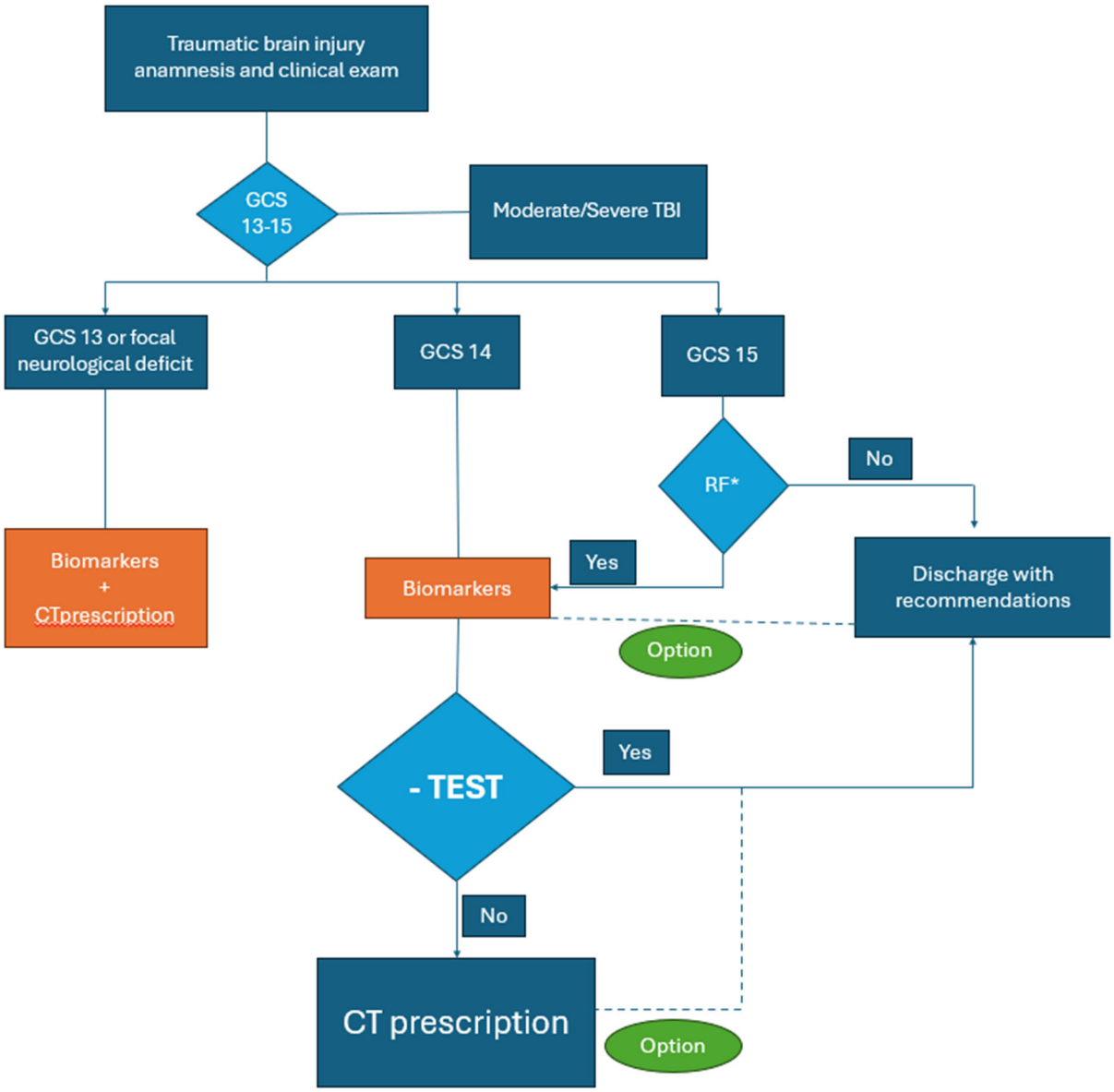
5. BRAINI2-IMPLEMENTATION PROCEDURE

5.1. STUDY ENROLLMENT METHOD AND FEASIBILITY

Use of the biomarkers GFAP and UCH-L1 being part of the 2023 guidelines for management of mTBI in Spain, and being now included in the new clinical management pathway in the hospital 12 de Octubre, all patients with mTBI admitted to the ER of the study site and answering to inclusion and exclusion criteria of the study will be considered for participation in this study. All patients assessed for mTBI will be considered for inclusion in the mTBI management bundle. This bundle of care, already accepted in the Department will include obtention of blood biomarkers by venepuncture. Patient management will not be altered by the study. De-identified patient data will be obtained from the clinical records and will be studied. All data obtained is recorded for the normal management of mTBI patients and therefore no extra information will be obtained. No further contact with the patient will be made outside of their normal interactions at the Hospital and with their general practitioner. Records from the electronic clinical records will be the only source of data in this study both in the acute setting and in the follow up of the patients.

5.2. STUDY TIMELINE AND PLANNED MANAGEMENT ALGORITHM

All patients with TBI admitted to the ER and with a GCS between 13 and 15 will receive a blood test for biomarker determination upon admission. All patients with GCS of 13 or with a focal neurological deficit on admission will receive a CT. CTs could be performed to GCS14 and 15, independently of the result of the combined test, but the results of the test will be taken into consideration to guide for prescribing a CT. The attending physician will be responsible for the management of the patient and will have to determine the reason to prescribe CT despite normality of the biomarker test. The management algorithm that is recommended is as follows:



Risk factors (RF) include:

-Loss of consciousness.

-Postraumatic amnesia (anterograde or retrograde).

-Advanced age (over 65)

-Antithrombotic treatment including platelet inhibitors.

-Difficulty in assessing level of consciousness: Cognitive impairment, intoxication.

-Persistent symptomatology: Repeated vomiting, persistent headache.

-High energy or High-risk mechanism: Falls over one's height, car accident, pedestrian involved in traffic accident, or accidents in which other there are other seriously injured patients.

Data will be collected directly from a specified structured form in the electronic health record of the patient. All data will be pseudonymised. Information regarding follow up will be recorded from the electronic health record regarding new contacts with the hospital or need of further assessment.

5.3. PARAMETER ASSESSMENTS

5.3.1. Clinical parameters

1) Vital signs will be measured in the emergency department according to standard practice (GSC score, arterial blood pressure, heart rate, respiratory rate, body temperature, pulse oximetry). The presence of vomiting, nausea or headache will be recorded, as well as the presence of loss of consciousness. All recorded variables will be obtained following the standard of care of the workup of the mTBI patient stablished in the Hospital and no extra information will be obtained.

Secondary deterioration within the first week after TBI will be obtained by reviewing electronic medical history of the patient´s and new contacts during this week with the ER, and is defined as follows:

· a decrease in GCS score of more than 2 points from the initial GCS score in the absence

of sedatives

· a deterioration in neurologic status sufficient to warrant intervention, i.e. mechanical

ventilation, sedation, osmotherapy, neurosurgical procedure or admission to the intensive care unit.

· Admission to a hospital ward exclusively related to deterioration of neurological condition due to TBI.

5.3.2. Biological assessments (BA)

Blood samples will be drawn only for the management of patients with mTBI, as established by the mTBI care bundle and within 12 hours after TBI. The volume of blood collected will be that necessary to obtain results for both GFAP and UCH-L1 biomarkers. Permission for obtention of this blood sample will follow the normal standard of care of any other blood sample obtained in the ER. For normal health care management of patients admitted due to mild TBI in which a CT scan is going to be performed, laboratory analysis regarding hemogram and formula, coagulation status (Prothrombin time (PT), INR and aPTT) and conventional biochemistry analysis (Na, K, glycemia, creatinine, AST and ALT) are normally obtained by local laboratories as a standard of care. These data of the conventional laboratory analysis performed to these patients as standard of care will be obtained and stored in the eCRF.

5.3.3. DATA COLLECTION AND DATA MONITORING

Data obtained as standard of care for the management of mTBI will be collected in the electronic clinical records. The Electronic Health Record is an essential tool for clinical decision-making and data collection, as it enables accurate and systematic documentation of patient information. However, its full potential is exploitable and useful when the data is structured. For this reason, and since the TBI information will be collected in the HER(Electronic Health Record), the hospital's IT data area improved the structuring and standardization of the information in the EHR. To this end, the mTBI diagnostic code was unified and codified (SNOMED CT) and a form was created with the questions that are asked when attending a patient with TBI. The completeness of the defined diagnosis together with the designed form will allow the identification of the cohort of patients with mTBI. In addition to the data included in the form, the study will collect demographic and baseline information at admission, the reason to prescribe brain CT scan and immediate CT findings by the local radiologist, biological data if indicated by the in-charge physician.

At 10 days postTBI, clinical research associates will review all information regarding the neurological status of the patients and the need for hospitalisation or other contacts to the ER in relation to mTBI. This review will be done thanks to the previous automatic extraction of the mTBI data collected in the EHR.

Regular quality checks on the information consigned in the EHR by attending physicians will be performed as a program for quality improvement of mTBI bundle. This program has been already run by the Department of Neurosurgery in order to enhance the recording of structured data in clinical records in our hospital. For this purpose, a dashboard in Power Business Inteligence (PowerBI) has been designed. In addition to functioning as an instrument for monitoring data recording, this PowerBi dashboard will also show the indicators outlined below for the purpose of protocol evaluation. These are time of care in the emergency department for patients with mTBI, percentage of CT requested, percentage of CT requested

in patients with negative biomarkers, percentage of CT requested in patients with positive biomarker, percentage of pathologic CT in patients with positive biomarker, percentage of pathologic CT in patients with negative biomarker, percentage of patients requiring admission and percentage of second ED visit after discharge.

Finally, the de-identified data from the mTBI cohort will be obtained and transferred into a web based electronic CRF(eCRF) built on RedCap to be able to be analysed. The database in RedCap will contain pseudo-anonymised clinical information about the patients with mTBI from six months prior to the implementation protocol and information from six months of the implementation protocol.

5.3.4. CT SCAN ANALYSIS

Brain CT scans are performed as part of the patient standard of care. CT scan findings are classified as CT negative or CT positive by local reviewers.

The criteria for CT positivity are crucial because the primary objective is related to the CT results (positive/negative). Criteria for CT-positive findings are as follows: a CT scan classified as type II or greater according to the Traumatic Coma Databank classification (range I–V), or a CT scan with the presence of the following lesions: (1) epidural haematoma, (2) subdural haematoma, (3) subarachnoid haemorrhage, (4) intraventricular haemorrhage, (5) contusion, (6) petechial haemorrhage or (7) any finding related to diffuse axonal injury and depressed skull fracture. Linear skull fractures will be recorded but not used for the definition of CT positive lesions. Subdural hypodense hygromas, calcifications, ischemia will not determine a positive qualification. Nevertheless, all findings will be recorded by. Radiologist will be trained to assess CTs regarding the following classification.

Items that WILL classify CT as positive	Items that will NOT classify CT as positive
Epidural hematoma	Subdural hygroma
Acute or subacute subdural hematoma	Chronic subdural hematoma (no high intensity lesion inside the hematoma)
Indeterminate extra-axial hemorrhage	All parenchymal or extraparenchymal calcifications
Subarachnoid hemorrhage	Brain tumors
Intraventricular hemorrhage	Linear non-depressed fracture
Depressed cranial fracture	Cranial base fracture
Brain contusion (including high intensity/mixed lesions and hypodense lesions)	Pneumoencephalus
Intraparenchymal traumatic hematoma	Hypodense chronic Ischemic lesions
Brain swelling	Facial fractures
Petechial hemorrhage	Scalp injury
Gliding contusions	
Signs of traumatic axonal injury (hyperdense lesions in brainstem or corpus callosum)	
Brain Swelling or oedema	
Compressed cisterns	

6. STUDY STOPPING RULES

6.1. STUDY STOPPING CRITERIA FOR A PARTICIPATING SUBJECT

Participants will be excluded from the study and replaced in case of a violation of an inclusion criterion, e.g. in the mTBI group: no mild TBI, no CT scan when the patient should have received one according to the study design, no blood sampling or after 12 hours post-injury.

7. STATISTICAL CONSIDERATIONS

7.1. SAMPLE SIZE

The primary endpoint of the study is to replicate the diagnostic performance of the VIDAS TBI assay to predict whether the tested patient would be positive or negative from brain injury visible on head CT scan and to determine that implementation of the VIDAS TBI, in the standard of care of patients with mTBI, is not associated with serious side effects during the six-month period of the study. We expect to test during a six-month period around 1000 patients (from the 3500 patients with suspected TBI that are admitted to our hospital yearly approximately (data from discharge diagnosis of patients with TBI related diagnostic codes)). With this sample size and with an expected prevalence of 10% of CT positivity we expect to have at least 100 patients with positive CTs. With this sample size we expect to replicate the NPV of the BRAINI study with an expected lower bound of the 2-sided 95% CI greater than or equal to 97.0%.

7.2. STATISTICAL ANALYSIS

7.2.1. DATA ANALYSIS RESPONSIBILITY

SERMAS will be responsible for the data analysis for the primary study objective (performance evaluation of the VIDAS TBI assay) in collaboration with BioMérieux. Data analysis for the secondary objectives will be performed by SERMAS.

7.2.2. DATA RETENTION

The site must retain its clinical trial records relating to the trial for at least 3 years after the clinical trial is completed or terminated.

7.3. STUDY PARTICIPANT CONFIDENTIALITY

Gathering and processing of personal data will be done in keeping with article 9 of European Regulation on data protection 2016/679 (General Data Protection Regulation) and the counsel on data Protection of 27th April 2016. It will follow the Spanish Organic Law on Personal data Protection 3/2018.

To protect the participant‘s confidentiality, data will be pseudonymised.

ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in accordance with the Declaration of Helsinki (amended at Fortaleza in 2013; for full version see http://www.wma.net), Good Clinical Practice Guidelines (GCP, ICHE6) and all applicable local regulations.

The study will only begin after receiving the approval of the local ethics committee and the waiver of specific informed consent, as the practice will be following standard management of TBI.

The Principal Investigator is responsible for ensuring compliance with these regulations, and adherence to protocols that have been approved by the ethics committee.

7.4. STUDY REGISTRATION

This study will be registered in the clinical trials registry: http://clinicaltrials.gov/ before its beginning.

8. SUBJECT RISKS AND BENEFITS

8.1. FORESEEBLE RISKS AND THEIR MINIMIZATION

No therapeutic interventions will take place in the context of the implementation studies. Diagnostic interventions include blood sampling, outcome assessments and CT imaging. All of them will be based on activities performed for the actual management of mTBI in the Hospital and accepted and promoted by different medical societies in our country. CT imaging is performed as a standard of care. Blood sampling for biomarker assessment and/or other determinations will be performed depending on clinical indication by the attending physician and related to the accepted protocol for managing mTBI.

8.2. POTENTIAL BENEFITS OF PROPOSED RESEARCH

There is no direct benefit for the patients. The results will be directly relevant to society in general and to future patients who suffer mTBI and will help policy makers to promote the mTBI bundle of care devised in our hospital.

The results of this study could have a major impact on the management of patients with TBI: 1) By reducing the number of unnecessary CT scans; 2)by improving management of patients being at risk as patients testing positive could be managed in a more urgent way(those patients with more probability of having a lesion in CT); and 3)by a more objective management of patients.

8.3. ADVERSE EVENTS

No structured adverse event reporting will be implemented. However, we will capture any serious complication which may occur during the clinical course in the CRF and analysing the clinical records.

9. ARCHIVING OF DOCUMENTS AND STUDY DATA

In accordance with Good Clinical Practice the following documents related to this research are to be archived:

By the physician investigators:

- for a period of 15 years following the end of the study

The protocol and any amendments to the protocol

The case report books

The source files of all included participants

All other documents and correspondence relating to the study

All these documents are the responsibility of the investigator during the archiving period.

By the sponsor:

- For a period of 15 years following the end of the study

The protocol and any amendments to the protocol

All other documents and correspondence relating to the study

All these documents are the responsibility of the sponsor during the archiving period.

No displacement or destruction of documents or data can be carried out without the agreement of the sponsor. At the end of the regulatory archiving period, the sponsor will be consulted concerning destruction. All data, documents and reports may be subject to audit or inspection.

10. PROTOCOL MODIFICATIONS

A substantial change is a modification likely to have a significant impact on the protection of the study participants, on the validity of the study or its results, on the interpretation of scientific documents that support the study design or conduct. A substantial change is subject to a written amendment submitted to the sponsor.

All amendments are validated by the sponsor, and by all study stakeholders. Prior to its implementation, the sponsor must obtain a favourable opinion from the ethics committee (CPP). All investigators will be informed of any amendment to the study protocol.

11. PROVISIONAL STUDY CALENDAR

-Staff training and technology deployment: January_March 2025

-Start of inclusions: April 2025

- Length of inclusion period: 6 months

- End of inclusions: September 2025

- Length of participation of each subject: 10 days

- Total length of the study: 12 months

12. COMMUNICATION AND PUBLICATION RULES

Data analysis will result in a written report that will be submitted by the sponsor, who shall submit it to the ethics committee. Any written or oral communication of research results must receive prior approval of the coordinating investigator and of any committee established for the research. The publication of the main results must indicate in the acknowledgements the name of the sponsor and investigators, methodologists, biostatisticians and data managers who substantially participated in the research, and the name of the funding source. The name of any person contributing to writing or editing the manuscript, if not already in the author list, should also be given in the acknowledgements. Publication will follow international standards of writing and publishing (The Uniform Requirements for Manuscripts of the ICMJE, April 2010) and respect the criteria for authorship.

13. PARTNERSHIP

The BRAINI2 study has received financial support from the European Institute of Innovation and Technology (EIT Health) for the business plan 2022-2024. SERMAS (Hospital Universitario 12 de Octubre and FIBH12O Madrid), Grenoble University Hospital (CHUGA) and the University Grenoble Alpes, Institút Catalá de la Salut (Hospital Váll D´Hebron), Hospital of the Technical

University of Munich (TUM Klinikum), CHU Nantes, CHU-Clermont-Ferrand, Luzerner kantosspital, association Daño Cerebral Invisible and BioMérieux are partners to conduct the project.

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15. APPENDIXES

Appendix 1: mTBI bundle of care.

These documents are available in separate files.