Outcome Prognostication of Acute Brain Injury using the Neurological Pupil Index (ORANGE) study: protocol for a prospective, observational, multicentre, international cohort study

Mauro Oddo,1,2 Fabio Taccone,3 Stefania Galimberti,4,5 Paola Rebora,4,6 Giuseppe Citerio,7 on behalf of the Orange Study Group

ABSTRACT

Introduction The pupillary examination is an important part of the neurological assessment, especially in the setting of acutely brain-injured patients, and pupillary abnormalities are associated with poor outcomes. Currently, the pupillary examination is based on a visual, subjective and frequently inaccurate estimation. The use of automated infrared pupillometry to measure the pupillary light reflex can precisely quantify subtle changes in pupillary functions. The study aimed to evaluate the association between abnormal pupillary function, assessed by the Neurological Pupil Index (NPI), and long-term outcomes in patients with acute brain injury (ABI).

Methods and analysis The Outcome Prognostication of Acute Brain Injury using the Neurological Pupil Index study is a prospective, observational study including adult patients with ABI requiring admission at the intensive care unit. We aimed to recruit at least 420 patients including those suffering from traumatic brain injury or haemorrhagic strokes, over 12 months. The primary aim was to assess the relationship between NPI and 6-month mortality or poor neurological outcome, measured by the Extended Glasgow Outcome Score (GOS-E, poor outcome=GOS-E 1–4). Supervised and unsupervised methods and latent class mixed models will be used to identify patterns of NPI trajectories and Cox and logistic model to evaluate their association with outcome.

Ethics and dissemination The study has been approved by the institutional review board (Comitato Etico Brianza) on 16 July 2020. Approved protocol V.4.0 dated 10 March 2020. The results of this study will be published in peer-reviewed journals and presented at conferences.

Trial registration number NCT04490005.

INTRODUCTION

Pupillary examination, including pupillary light reactivity (PLR), is a fundamental part of the clinical examination in patients suffering from acute brain injury (ABI), with both diagnostic and prognostic values.1 As an example, the oculomotor nerves might be compressed due to displacement of the brainstem, and clinicians have accepted fixed and dilated pupils as part of the ‘herniation’ syndrome. Elevated intracranial pressure (ICP) may alter midbrain function and cause abnormalities in pupil size, symmetry and PLR.2–5 Sustained or newfound pupillary abnormalities are associated with a worse outcome,6 and indeed PLR is a robust validated predictor in several prognostic models, such as the Corticosteroid Randomization after Significant Head Injury and the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) scores.7 However, in current clinical practice, the pupillary examination is performed using a manual, hand-held light source (eg, pen torch), implying that the evaluation of pupillary size and reactivity remains essentially based on a visual qualitative assessment. This traditional approach has several limitations, such as limited precision (eg, due to small pupil size or specific administered treatments), significant intraobserver and interobserver variability, differences in ambient light exposure between measurements or the technique used to direct the stimulus (ie, intensity, proximity, duration and orientation of the light source).8–10

Strength and limitation of this study

- The study will cover the more common neurological emergencies and, in a large population of patients with acute brain injury, the relationship between pathological Neurological Pupil Index and outcome.
- The standard data acquisition in the centres, transferred from the device into the eCRF, and the granularity of data will guarantee high-quality data.
- Due to the observational nature of our study, we will report only associations and not causality relationship.
Quantitative, automated, infrared technology for pupillary examination has been used for years in ophthalmology and anaesthesiology research. Its interest in neurocritical care has progressively grown, in parallel with the advancements in device technology. In this regard, the use of the non-invasive NPi–200 pupillometer (Neuroptics, Laguna Hills, California, USA) allows the measurement of a series of dynamic pupillary variables which can be integrated into an algorithm to compute the Neurological Pupil Index (NPI). The NPI is calculated by the handheld device using a set of variables including size, latency, constriction velocity and dilation velocity. Each variable, if measured from an individual pupil measurement is compared against the mean of a reference distribution of healthy subjects, taking the difference and then standardising it by the corresponding SD. Finally, the sets of all healthy subjects are combined to fall into a scale set between 0 and 5 (with a 0.1 decimal precision), with an NPI value of <3 indicating abnormal pupillary reactivity. NPI is not influenced by sedation–analgesia, at the doses used in neurocritical care practice, and by mild hypothermia. Preliminary single-centre data recently demonstrated that abnormal NPI is associated with worse outcome in patients with traumatic and haemorrhagic ABI, and can be a useful adjunct for ICP monitoring and response to therapy. There is currently a great need for quantitative tools to predict early prognostication in patients with ABI, and the NPI appears of potentially great value.

For this purpose, large multicentre studies are required. We recently conducted an international multicentre study that demonstrated the prognostic value of NPI in the setting of early prognostication of ABI following cardiac arrest. Given the encouraging results, we decided to enlarge the spectrum of ABI diseases monitored with NPI in a new study. Here, we aim at evaluating the prognostic value of the NPI in patients with ABI following traumatic brain injury (TBI), aneurysmal subarachnoid haemorrhage (SAH) or intracerebral haemorrhage (ICH) at risk of secondary ICP elevation.

Objectives
The primary aim of the study was to evaluate the association between abnormal NPI and long-term outcomes (ie, 6-month mortality and neurological outcome, measured using the Extended Glasgow Outcome Score (GOS-E)) in patients with ABI.

The secondary aim, in patients with ICP monitoring, was to evaluate the relationship of abnormal NPI and ICP following ABI.

METHODS AND ANALYSIS

Study design and setting
This is a prospective, observational cohort study involving 13 centres worldwide that routinely use pupillometry. Recruitment will last 12 months, and patients will be followed up for 6 months.

Study population
Consecutive participants will be recruited at the participating centres according to the inclusion and exclusion criteria reported as follows.

Inclusion criteria
- Intensive care unit (ICU) admission after ABI, including TBI, SAH and ICH requiring intubation and ventilation for neurological reasons/deterioration.
- Age ≥18 years old.
- Pupillometry is available as a standard evaluation tool.

Exclusion criteria
- Facial trauma not allowing pupils’ evaluation.

Screening and data collection
All patients admitted to the participating ICUs after ABI will be screened daily and entered into a screening log (online supplemental appendix, Screening Log–Registry). Each ICU will recruit consecutive eligible patients and collect data for each included patient daily in an expanded electronic CRF developed in REDCap (online supplemental appendix, eCRF).

Both common data elements and aetiology-specific data will be recorded. Demographic characteristics and medical history information will be extracted from patients’ medical records including gender, age, comorbidities, diagnosis, timeline and clinical presentation of ABI. All NPI and ICP data, as well as additional neuromonitoring and neuroimaging data, will be extracted from patients’ medical records too and documented in the eCRF. The patients admitted to the units will be screened by research staff, and the pupillometry evaluation, part of the clinical practice in all the centres, will be performed by trained staff. The two eyes’ specific NPI and the matched ICP will be collected every 4 hours from admission up to day 7. Data collected will also include additional ICP-derived variables (eg, ICP max, ICP 20 index: number of end hourly measures of ICP of >20 mm Hg divided by the total number of measurements, multiplied by 100) and interventions (eg, osmotherapy, therapy intensity level and neuroimaging). The GOS-E will be collected at ICU/hospital discharge and 6 months from ICU admission. The latter will be collected via telephone-structured interviews with patients and/or family members using a validated questionnaire. In case of death, details on the cause and date will be collected as well.

Sample size and statistical analysis
As no data on NPI trajectory in time and its association with outcome is available for sample size calculation, we referred to pupil reactivity as a proxy of NPI behaviour and to results of a study recruiting patients with similar characteristics (Intracranial Pressure monitoring in the ICU: An International Prospective Observational Study on Intracranial Pressure in Intensive Care, trial registration number: NCT03257904). Assuming a 6-month mortality of 53% in patients with one or both unreactive pupils and 29% in patients with both reactive pupils, a sample of 420 patients is needed to be powered for the study. This is based on a two-tailed test at 5% significance level, a 10% loss to follow-up and a 75% power value.
patients achieves 94% power to detect a HR of nearly 2 at a 0.05 significance level. As far as recruitment, each of the 13 centres involved in the study is expected to include nearly 35 patients in a recruitment period of 1 year, and this is in line with their potentiality of recruitment for the three pathologies that is of at least 80 patients per year.

Qualitative variables will be summarised by counts and percentages, while quantitative characteristics will be summarised by quartiles or mean and SD, as appropriate. Supervised and unsupervised methods (eg, pattern recognition and cluster trajectory analyses) will explore the possibility to identify patterns of NPI trajectories associated with different prognosis on the individual NPI longitudinal measurements. NPI trends will be also modelled by longitudinal mixed models using splines and latent class mixed models.

A Cox and a logistic model will be applied to evaluate the association between the NPI process and the 6-month mortality and neurological recovery (GOS-E≤4 vs GOS-E>4) at 6 months, respectively. This will be done considering NPI in categories that identify different potential patterns in NPI longitudinal profiles or using summary measures that have been already introduced in this context, such as the percentage of NPI≤3 observed in the time course or the area under the trajectory in time. This analysis will be done both overall, on a multivariable model that will explore the interaction with the different pathologies, and on the three specific pathologies. A longitudinal linear model that will explore the interaction with the different pathologies, and on the three specific pathologies of at least 80 patients per year.

The two eyes will contribute to these analyses with the worst result only and with their absolute NPI difference, but multivariate models will be also investigated to consider data from both eyes as a sensitivity analysis. To evaluate the association between NPI and ICP, a multivariable longitudinal linear model on the ICP20 index (percentage of end-hourly measures of ICP >20 mm Hg) will be applied on patients with ICP monitoring, both overall and on the three diseases. A longitudinal linear regression model on ICP values will be also considered. All the analyses will be performed in R.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

Limitations

The main limitation of this study is its observational nature, which makes it impossible to draw causal inferences reliably. We try to overcome this limitation with a preplanned statistical plan and a rigorous analysis of the findings.

ETHICS AND DISSEMINATION

This study will be conducted in compliance with the protocol V.4.0 dated 10 March 2020 approved by the ethics committee 'Brianza' at the ASST-Monza (approval date: 16 July 2020). Each National Coordinator will notify the relevant ethics committee, in compliance with the local legislation and rules. The approval of the protocol (if required by local authorities) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the three chief investigators before the changes are implemented into the study. In case of patients not able to provide an informed consent at the time of study recruitment, each country will refer to the local/national law on the matter of lack of capacity. Generally, if patients will regain capacity at the follow-up, they will be asked to provide the informed consent for the acute data and follow-up or deny further research participation without any objection against use for research of data collected during the acute phase or deny further research participation and require the destruction of acute data collected. The study will be performed according to the Helsinki Declaration and the International Conference on Harmonisation for Good Clinical Practice.

The study will be published in a peer-reviewed journal and presented at the main intensive care medicine scientific congresses. Authorship will be granted according to the International Committee of Medical Journal Editors (ICMJE) definitions.

The University of Milano–Bicocca has the property of all the data collected. The data reside at the University Milano–Bicocca as study sponsor; all procedures will comply with the EU regulation on data protection 2016/679 on the protection of natural persons regarding personal data processing and movement. Local site data will be co-owned by each participating centre, and they will be given access to local data for any scientific purpose on request. By entering data into the Outcome Prognostication of Acute Brain Injury using the Neurological Pupil Index (ORANGE) study database, each centre agrees that the chief can use these data for scientific purposes. Any requests for the use of the data set for subsequent studies will be made to the ORANGE study chief investigators. Any requests for the use of the data set for subsequent studies will be made to the ORANGE study chief investigators. A formal data monitoring committee is not needed since it is not an interventional controlled study. A dedicated staff from the University of Milano–Bicocca will monitor the data included in the eCRFs checking for inconsistencies.

Data confidentiality

Participant confidentiality is strictly held in trust by the participating investigators and their staff. All medical or administrative staff with access to the data is subject to a duty of confidentiality and data protection. Therefore, the study protocol, documentation, data and all other information generated will be held in strict confidentiality agreement protocols. The study sponsor and representatives of local authorities may inspect all documents and records required to be maintained by the local
investigator for the participants in this study. The clinical study site will permit access to such records.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to the Data Manager and the Statisticians of the study. For this purpose, data will be deidentified at input into the eCRF by the local centres/investigators. Individual participants and their research data will be identified by a unique study identification number. The eCRF system used by clinical sites and by research staff will be secured.

Lack of capacity and delayed consent
Patients recruited in this study will not be able to provide informed consent at the time of recruitment.22 Consent procedures will follow local policies.

At follow-up, patients who have regained capacity will be asked to provide informed consent and will be given the possibility to

► Provide informed consent for the acute data and follow-up.
► Deny research participation and request destruction of acute data collected.

Medical care related to the study
The medical care of the participant in the study is performed as per the local standard of care, without any deviation from clinical protocols. All the procedures follow the latest recommendations for ABI.

Premature termination or suspension of study
This study may be suspended or prematurely terminated for reasonable cause agreed by the investigators. Written notification, documenting the reason for study suspension or termination will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the local principal investigator will promptly inform the ethics committees or other local authorities according to local legislation and will provide the reasons for the termination or suspension. Circumstances that may warrant termination could be recruitment that will be prolonged for >5 years or insufficient compliance with the protocol. The study may resume when the concerns have been addressed and issues resolved.

REFERENCES


Outcome pRognosticatcion of Acute brain injury with the NeuroloGical pupil indEx

ORANGE

ClinicalTrials.gov Identifier: NCT04490005
## 1. Table of Contents

1. Table of Contents ................................................................................................................................. 2
2. Protocol Changes History ......................................................................................................................... 3
3. Investigators (in alphabetical order) .......................................................................................................... 3
4. Summary ................................................................................................................................................. 4
5. Introduction ............................................................................................................................................ 5
6. Research questions and Objectives ........................................................................................................ 5
7. Methods .................................................................................................................................................. 6
8. Sample size calculation ............................................................................................................................ 6
9. Screening .................................................................................................................................................. 6
10. Inclusion Criteria .................................................................................................................................... 6
11. Exclusion Criteria ................................................................................................................................... 6
12. Demographics and Medical History ....................................................................................................... 7
13. NPI Data and Daily eCRF ....................................................................................................................... 7
14. Outcome measures ................................................................................................................................. 7
15. Distribution of the Information ................................................................................................................ 7
16. Timeline ................................................................................................................................................ 7
17. Endorsement, Funding & Methodological Support ............................................................................... 7
18. Potential Risks and Benefits ................................................................................................................... 8
19. Risks ..................................................................................................................................................... 8
20. Benefits ................................................................................................................................................ 8
21. Access to data ......................................................................................................................................... 9
22. Source data .......................................................................................................................................... 9
23. Data confidentiality ................................................................................................................................. 9
24. Ethics/Protection of Human rights ......................................................................................................... 10
25. Ethical standards ................................................................................................................................... 10
26. Ethics committee .................................................................................................................................. 10
27. Lack of capacity and Delayed Consent .................................................................................................. 10
28. Medical care related to the study .......................................................................................................... 10
29. Data collection and management responsibilities .................................................................................. 10
30. Study record retention .......................................................................................................................... 11
31. Responsibilities .................................................................................................................................... 11
32. Chief investigators ............................................................................................................................... 11
33. Co-investigators ................................................................................................................................. 11
34. Site investigators ............................................................................................................................... 11
35. Publication and data sharing policy ....................................................................................................... 12
36. Data sharing policy ............................................................................................................................. 12
37. Publication and Authorship .................................................................................................................. 12
38. Expected impact of the study .............................................................................................................. 12
39. References ......................................................................................................................................... 13
40. Appendix – Screening Log ..................................................................................................................... 15
41. Appendix – eCRF ................................................................................................................................. 17
42. PATIENT ELEMENTS eCRF ............................................................................................................... 17
43. NPI and matched ICP daily DATA CAPTURE (Day 1 to 7) .................................................................... 21
44. CDEs - DISCHARGE STATUS eCRF ................................................................................................... 25
45. CDEs – FOLLOW-UP AND END OF STUDY eCRF ......................................................................... 27
46. Appendix 5 – Scales used in the eCRF .............................................................................................. 28

Orange protocol V 2.0 20Feb2020

2. Protocol Changes History

<table>
<thead>
<tr>
<th>Version</th>
<th>Description</th>
<th>Date</th>
<th>Authors/Reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td>V 1.0</td>
<td>First Draft Protocol</td>
<td>16/01/2020</td>
<td>MO/GC</td>
</tr>
<tr>
<td>V 1.1</td>
<td>Complete Protocol</td>
<td>19/02/2020</td>
<td>MO/GC/SG</td>
</tr>
<tr>
<td>V 2.0</td>
<td>Final Protocol</td>
<td>20/02/2020</td>
<td>MO/GC</td>
</tr>
</tbody>
</table>

3. Investigators (in alphabetical order)

Chief Investigators
Prof Giuseppe CITERIO, Università Milano - Bicocca, Italy
Prof. Mauro ODDO, Lausanne, Switzerland

Co-investigators
Prof Anselmo Caricato, Roma, Italy
Prof Fabio Silvio Taccone, Brussels, Belgium
Prof Frank Rasulo, Brescia, Italy
Prof Kjetil Sunde, Oslo, Norway
Prof Pierre Bouzat, Grenoble, France
Prof Rafael Badenes, Valencia, Spain
Prof Stefan Schwab, Erlangen, Germany
Invited (20.9.2020) Claude Hemphill, Jose Suarez

Statisticians
Prof Stefania Galimberti, Università Milano - Bicocca
Prof Paola Rebora, Università Milano - Bicocca

Scientific coordinator of the study

Name and Surname: Giuseppe Citerio
Academic title: Associated Professor
Department: School of Medicine, Dept. of Medicine and Surgery
Institute: University of Milano - Bicocca
City, Country: Monza (MB) - Italy

Signature
Date
### 4. Summary

<table>
<thead>
<tr>
<th>Title</th>
<th>Outcome pRognostication of Acute brain injury using the NeuroloGical pupil indEx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Title</td>
<td>O R A N G E</td>
</tr>
<tr>
<td>Study Design</td>
<td>Prospective, observational, multicentre, international, cohort study</td>
</tr>
<tr>
<td>Sponsors</td>
<td>University of Milano - Bicocca</td>
</tr>
</tbody>
</table>

**Objectives**

The primary aim is to evaluate the association between abnormal Neurological Pupil index (NPI) and long-term outcome (6-month mortality and neurological recovery, measured with the extended Glasgow Outcome Score, GOS-E) in patients with acute traumatic and haemorrhagic acute brain injury (ABI).

The secondary aim, in patients with ICP monitoring, is to evaluate the relationship of abnormal NPi and intracranial pressure following acute traumatic and haemorrhagic ABI.

**Methods**

This international multicentre prospective observational study aims to recruit >400 patients admitted to intensive care units.

**Inclusion Criteria:**

- Intensive care unit (ICU) admission following traumatic brain injury (TBI), aneurysmal subarachnoid haemorrhage (SAH) and intracerebral haemorrhage (ICH) requiring intubation and ventilation for neurological reasons/deterioration.
- Age >18 years old.
- Pupillometry available as standard evaluation tool at study centre.

**Exclusion Criteria:**

- ABI not admitted to the ICU
- ABI not requiring intubation and ventilation for neurological reasons/deterioration.
- Facial trauma not allowing pupils' evaluation
- Age <18 years

**Outcome measures:** Glasgow Outcome Scale-Extended at 6 months.

**Endpoint:** The primary endpoint of the study is to evaluate the prognostic performance of the NPi in predicting patient long-term outcome (6-month mortality and neurological recovery, measured with the extended Glasgow Outcome Score, GOS-E).

**Duration of the study**

18 months, including 12-month of recruitment based on 70 patients/centre plus 6 months GOS-E follow-up.

**Funding**

Unrestricted grant by Neuroptics®.
5. Introduction

Pupillary examination, and in particular pupillary light reactivity, are fundamental for intensive care unit (ICU) monitoring and follow-up of patients with acute brain injury (ABI) having both diagnostic and prognostic values [1]. Secondary cerebral insults, e.g. elevated intracranial pressure (ICP), may alter midbrain function and cause abnormalities in pupil size, symmetry and pupillary light reactivity [2-5]. Sustained or newfound pupillary abnormalities are associated with a worse outcome [6], and indeed pupillary light reactivity is a robust validated predictor in several prognostic models, such as the CRASH (Corticosteroid Randomization after Significant Head Injury) and the IMPACT (International Mission for Prognosis and Analysis of Clinical Trials) scores [7]. In current clinical practice however, pupillary examination is performed using a manual, hand-held light source (e.g. pen torch), implying that the evaluation of pupillary size and reactivity remains essentially based on a visual qualitative assessment. This traditional approach has several limitations, such as limited precision (especially in patients with small pupil size), significant intra- and inter-observer variability, differences in ambient light exposure between measurements, or the technique used to direct the stimulus (i.e. intensity, proximity, duration and orientation of the light source) [8-10].

The use of quantitative, automated, infrared technology for pupillary examination has long been used in ophthalmology and anesthesiology research [4, 11, 12]. Its interest in neurocritical care has progressively grown [13], in parallel with the advancements in device technology. In this regard, the use of the non-invasive NPi®-200 pupillometer (Neuroptics, Laguna Hills, CA, USA) allows the measurement of a series of dynamic pupillary variables (including the percentage pupillary constriction, latency, constriction velocity, and dilation velocity), which can be integrated into an algorithm, to compute the Neurological Pupil index (NPi). The NPi is a proprietary scalar index with values between 0 and 5 (with a 0.1 decimal precision) [2], an NPi value < 3 indicating an abnormal pupillary reactivity [2, 3, 14]. Importantly, the NPi is not influenced by sedation-analgesia, at the doses used in neurocritical care practice, and by mild hypothermia [2, 3, 14]. Preliminary single-center data recently demonstrated that abnormal NPi is associated with worse outcome in patients with traumatic [15] and hemorrhagic ABI [16, 17], and can be a useful adjunct for ICP monitoring [15] and therapy [18]. There is currently a great need for quantitative tools to predict early prognostication in ABI patients, and the NPi appears of potential great value in this setting [19]. For this purpose, large multicenter studies are required. We recently conducted an international multicenter study that demonstrated the prognostic value of NPi in the setting of early prognostication of ABI following cardiac arrest [20]. Here, we aim at evaluating the prognostic value of the NPi in patients with ABI following traumatic brain injury (TBI), aneurysmal subarachnoid hemorrhage (SAH) or intracerebral hemorrhage (ICH) at risk of secondary ICP elevation.

6. Research questions and Objectives

Research questions

We hypothesize that:

a) Abnormal NPi (defined as NPi <3) are strongly predictive of poor GOS-E (1-4) at 6 months after the acute event.

b) NPi=0 is strongly predictive of mortality (GOS 1).

c) Abnormal NPi is predictive of a higher ICP 20 index (number of end-hourly measures of ICP >20 mm Hg divided by the total number of measurements, multiplied by 100) and a greater burden of interventions needed to control ICP (measured by the Therapy Intensity Level scale for ICP management, TIL 4) [21].
Objectives

- **The primary aim** is to evaluate the association between abnormal Neurological Pupil index (NPI) and long-term outcome (6-month mortality and neurological recovery, measured with the extended Glasgow Outcome Score, GOS-E) in patients with acute traumatic and haemorrhagic ABI.
- **The secondary aim**, in patients with ICP monitoring, are to evaluate the relationship of abnormal NPI and intracranial pressure following acute traumatic and haemorrhagic ABI.

7. Methods

Prospective, observational, international cohort study focussed at identifying the relationship of NPI with:

- long-term outcome defined as 6-month mortality and neurological recovery, measured with the extended Glasgow Outcome Score, GOS-E;
- intracranial hypertension.

Sample size calculation

No formal sample size calculation has been performed due to the exploratory nature of the study. However, we expect to recruit a total of 420 patients, 140 per pathology (i.e. TBI, ICH, SAH), over a 12-months period. Therefore, the six participating centres will contribute, based on their potentiality of recruitment, with a minimum of 20 patients for each of the three pathologies, for a total of 60.

Screening

All patients admitted to the participating ICUs in coma after ABI will be screened daily and entered into a screening log (Appendix- Screening Log - Registry). Each ICU will recruit eligible patients for 12 consecutive months and collect data for each recruited patient daily in an expanded electronic CRF (Appendix-eCRF). Both common-data elements and aetiology-specific data will be collected.

Inclusion Criteria

- Intensive care unit (ICU) admission following traumatic brain injury (TBI), aneurysmal subarachnoid haemorrhage (SAH) and intracerebral haemorrhage (ICH) requiring intubation and ventilation for neurological reasons/deterioration.
- Age >18 years old.
- Pupillometry available as standard evaluation tool at study centre.

Exclusion Criteria

- ABI not admitted to the ICU.
- ABI not requiring intubation and ventilation for neurological reasons/deterioration.
- Facial trauma not allowing pupils’ evaluation.
- Age < 18 years
Demographics and Medical History
Demographic characteristics and past medical history information will be extracted from patients’ medical records including gender, age, co-morbidities, diagnosis, timeline and clinical presentation of acute brain injury (Appendix-eCRF). All NPi and ICP monitoring data, as well as additional neuro-monitoring and neuroimaging data will be documented in the eCRF (Appendix-eCRF).

NPI Data and Daily eCRF
The daily eCRF Data Capture will be completed for NPi (collected every 4 hours) and for ICP (matched to NPi), every day, from admission up to day 7 (Appendix-eCRF). Data collected will also include additional ICP-derived variables (ICP 20 index, ICP max) and interventions (osmotherapy, TIL 4, neuroimaging).

Outcome measures
Centres will collect the Glasgow Outcome Scale-Extended (GOS-E) as main outcome measure in the CDEs Discharge Status (GOS-E at ICU/hospital discharge) and End-of-Study eCRF (GOS-E at 6 months, Appendix 3). Data on the cause of death will be collected as well. The GOS-E at the End-of-Study will be collected via telephone-structured interviews to patients and/or family members using a validated questionnaire [22].

Distribution of the Information
The study will be published in a peer reviewed journal and presented at main intensive care medicine scientific congresses.

Timeline

<table>
<thead>
<tr>
<th></th>
<th>03/2020</th>
<th>04/2020</th>
<th>07/2020</th>
<th>12/2021</th>
<th>02/2022</th>
<th>04/2022</th>
<th>06/2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol finalization</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC submission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eCRF development</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Patient enrolment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Data completion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Manuscript preparation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Presentation of results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

8. Endorsement, Funding & Methodological Support
Supported by an unrestricted grant from Neuroptics®.
Methodological support: Biostatistics Unit at Bicocca Bioinformatics Biostatistics and Bioimaging Centre - B4.
9. Potential Risks and Benefits

Risks
The ORANGE study is observational. It does not introduce any interventional procedure. The data is extracted from the patients’ medical records and does not affect local standard of care. Hence, the study does not add any interventional risk to the patients recruited. Confidentiality breach is a potential risk, which will be addressed by anonymization of data and centre-initiated allocation of progressive unique identifiers to centres and patients recruited.

Benefits
The potential benefit of the study consists in improving the knowledge for a better medical care for similar patients in the future and the generation of hypotheses for further collaborative research.

10. Premature termination or suspension of study
This study may be suspended or prematurely terminated for reasonable cause agreed by the Investigators. Written notification, documenting the reason for study suspension or termination will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the local PI will promptly inform the Ethics Committees or other local authorities according to local legislation and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination could be recruitment will be prolonged for > 5 years or insufficient compliance with the protocol. Study may resume when the concerns have been addressed and issues resolved.

11. Data Collection
ICUs willing to participate will register electronically and collect data via an electronic Case-Report Form (RedCAP platform, see Appendix-eCRF). An online training module will be developed to aid data collectors in completing the study eCRF. Data collection will be web based, permitting conditional Data Collection screens, i.e. data collectors will be automatically guided as to which sections to complete based on data entered indicating whether Inclusion Criteria are met.

12. Statistical methods
No formal sample size calculation has been performed due to the exploratory nature of the study. However, we expect to recruit a total of 420 patients, 140 per pathology (i.e. TBI, ICH, SAH), over a 12-months period. Therefore, the six participating centres will contribute, based on their potentiality of recruitment, with a minimum of 20 patients for each of the three pathologies, for a total of 60.

Data will be summarised by counts and percentages and quartiles or means and standard deviation, as appropriate, for qualitative and quantitative characteristics, respectively. Unsupervised and supervised methods will be applied with explorative purposes using the individual NPi longitudinal measurements. For example, the pattern recognition of longitudinal profiles and the cluster trajectory analyses will be used in order to identify patterns of NPi trajectories associated with prognosis. NPi trends will be also described graphically and modelled by longitudinal mixed models using splines.
A Cox and a logistic model will be then applied to evaluate the association between the NPi process with the 6-month mortality and the neurological recovery (GOSE≤4 vs GOSE>4) at 6 months, respectively. This will be done considering NPi in categories identifying different potential patterns in NPi profiles or using summary measures that have been already introduced in this context, such as the percentage of NPi<3 observed in the time interval of observation or the area under the trajectory in time. The two eyes will contribute to these analyses with the worst result. The improvement with respect to standard risk factors (i.e. the components of the IMPACT model for TBI patients) will be also evaluated by multivariable models.

Lastly, the association between NPi and mortality will be evaluated by the use of shared frailty joint models, in which NPi trend in left and right eye will be evaluated by a multivariate mixed model, which outcome will be used to model mortality [23]. Model-based mortality prediction will be computed based on individual NPi trends. The same kind of approach will be used for the binary outcome.

The main analyses will be performed overall and by specific pathology.

13. Source documents and access to source data/documents

Access to data

The University of Milano – Bicocca has the property of all the data collected. The data resides at the University Milano-Bicocca as study Sponsor; all procedures will comply with the EU regulation on data protection 2016/679 on the protection of natural persons regarding personal data processing and movement. Local site data will be co-owned by each participating centre, and they will be given access to local data for any scientific purpose upon request. By entering data into the ORANGE study database, each centre agrees that the chief can use these data for scientific purposes. Any requests for the use of the data set for subsequent studies will be made to the ORANGE study chief investigators. Any requests for the use of the data set for subsequent studies will be made to the ORANGE study chief investigators.

Source data

Source data include all information, original records of clinical findings, observations, or other activities in the research necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to: hospital records, clinical and office charts, laboratory notes, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-Rays and participant fliers and records kept at laboratories, and medico-technical department involved in the study.

Data confidentiality

Participant confidentiality is strictly held in trust by the participating investigators and their staff. All medical or administrative staff with an access to the data is subject to a duty of confidentiality and data protection. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidentiality agreement protocols. The study sponsor and representatives of local authorities may inspect all documents and records required to be maintained by the local investigator for the participants in this study. The clinical study site will permit access to such records.
Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to the Data Manager and the Statistician of the study. For this purpose, data will be deidentified at input into the eCRF by the local centres/investigators. Individual participants and their research data will be identified by a unique study identification number. The eCRF system used by clinical sites and by research staff will be secured and password protected.

14. Ethics/Protection of Human rights

Ethical standards
The study will be conducted in full conformity with the Declaration of Helsinki and Good Clinical Practices.

Ethics committee
Each investigator will notify the relevant ethics committee, in compliance with the local legislation and rules. The approval of the protocol (if required by local authorities) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the two chief investigators before the changes are implemented to the study.

Lack of capacity and Delayed Consent
Patients recruited in this study will not be able to provide informed consent at the time of recruitment (see 6.3. Inclusion Criteria). The responsible clinical/research staff will act as Consultee and consent eligible patients after discussion with the next-of-kin.
If the patient has a Power of Attorney or a Legal tutor or an, he/she will act as Consultee and will be asked to consent/decline participation to the study on legal behalf of the patient.
If patients have Advance Decision Plan including participation in research studies the Plan will be respected and recruitment pursued/abandoned accordingly.
At follow-up, patients who have regained capacity will be asked to provide Informed Consent and will be given the possibility to:
• Provide Informed Consent for the acute data and follow-up.
• Deny research participation and request destruction of acute data collected.

Medical care related to the study
The medical care of the participant in the study is performed as per local standard of care, without any deviation from clinical protocols. All the procedures that are suggested to the investigators are in accordance with the latest recommendations for Acute Brain Injury. The outcome measure (GOS-E) is a validated measure of neurological outcome. Therefore, the present study is an observational study without any specific intervention.

15. Data handling and record keeping

Data collection and management responsibilities
The data resides at Milano - Bicocca University. All procedures will comply with the EU regulation on data protection 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.
All data recorded and collected cannot be linked to the subject who supplied it. The patient is assigned a unique identifier number that will be used to identify the data. The patient’s identity will be kept locally, in the centre where the patient was included, under responsibility of the local investigator, together with an identification number and a copy of the data to answer queries during the process of database cleaning. Once the database is cleaned, the local investigator will destroy the material that links a patient’s identity to the identifier number.

Study record retention
All standard practices related to the locked storage, password-protected backup, and security of this data will be observed at each centre. Appropriate measures will be taken to protect the data against accidental or unlawful destruction or accidental loss, alteration, unauthorized disclosure or access, abuse, and against all other unlawful forms of processing.

16. Responsibilities

Chief investigators
The role and responsibilities of the Chief Investigators are:
• to coordinate the study and identify participating countries and country coordinators.
• to ensure that the study is conducted in accordance to the protocol and in compliance with GCP in all participating sites and countries.
• to apply for regulatory approval at a national level in the coordinating country and ensure that ethical committee (EC) approvals, or waivers of EC approvals, are obtained for all the participating sites in their country prior to the initiation of the study.
• to ensure application for regulatory approval from a local Data Protection Authority (DPA) in the coordinating country.
• to assist with the translation of the study documents according to local regulations.
• to ensure good communication with the participating country coordinators, including monitoring and encouraging to achieve optimal recruitment and follow-up during the period of the study.
• is the main responsible of the collected data, statistical analysis, communication and publications.

Co-investigators
The role and responsibilities of the co-investigators are:
• to apply for regulatory approval at a national level where applicable and ensure that ethical committee (EC) approvals, or waivers of EC approvals, are obtained for all the participating sites in their country prior to the initiation of the study.
• to apply for regulatory approval from a local Data Protection Authority (DPA), where applicable.
• to assist with the translation of the study protocol, Patient Information Sheet, Consultee form or equivalent according to local regulations and CRF where required.

Site investigators
For each participating ICU, one local investigator is identified. The role and responsibilities of the local investigators are:
• to lead the study at their site.
• to inform the respective country coordinator of their interest to participate in the study.
• to apply for ethical approval and/or local site approvals in collaboration with the country coordinator and ensure that local approvals are in place prior to the initiation of the study.
• to notify and send scanned copies of local sites approval to the country coordinator.
• to ensure accurate and timely data collection and entry in to the electronic Case Report Form (eCRF).
• to reply promptly to data queries from the country coordinator.
• to maintain effective communication with the country coordinator and coordinating centre.
• to inform the patient about his enrolment in the study and to require the patient's non-opposition according to local regulations

17. Publication and data sharing policy

Data sharing policy
Any requests for the use of the data will be made to the ORANGE study group, and decisions will be made in relation to these requests. The ORANGE study investigators will have priority in requests to use the data set for subsequent studies.

Publication and Authorship
Data will be made available to the scientific community by means of abstract submitted to main intensive care annual conferences and by scientific papers submitted to peer-reviewed journals. Authorship of the main manuscript will follow the ICMJE recommendations that base authorship on the following four criteria:
• Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
• Drafting the work or revising it critically for important intellectual content; AND
• Final approval of the version to be published; AND
• 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.
All the participant centres will be granted in the group authorship, “ORANGE”. The corresponding author will specify the group name and will clearly identify the group members who can take credit and responsibility for the work as collaborators. For each centre, a participant will be indicated in the group authorship list every 15 patients enrolled.

18. Expected impact of the study
The investigators expect to obtain data that will influence clinical practice and patient care, particularly with regard to severe ABI prognostication.
19. References


20. Appendix – Screening Log

Tool Summary Sheet

Tool: Site Screening and Enrollment Log
Purpose: To record the consent and screening of all subjects and the outcome of each screening.
Audience/User: Study Coordinators, Principal Investigators (PI), other site staff
Details: This log should provide a comprehensive list of all subjects who were screened for eligibility if the information is not maintained electronically.
Best Practice Recommendations: Record subjects as they are consented, to ensure completeness and accuracy of the data.

Include all subjects who were consented and screened, including screen failures.
This log should contain no identifying information. Subjects may be tracked separately on logs, such as a coded list with a key.
Number each page and maintain this log in the Essential Documents Binder, behind the ‘Screening/Enrollment Log’ tab. (Synonyms for this binder include Investigator Binder, Regulatory Binder, Investigator Site File (ISF), and Study File.)
Store pages in reverse chronological order, with the newest pages of the log placed at the front of the section.
At the conclusion of the study, identify the final page of the log by checking the box in the footer.
Remove this Tool Summary Sheet before use of the log.
<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Date of Consent</th>
<th>Version of Consent</th>
<th>Date Screened</th>
<th>Eligible for Enrolment?</th>
<th>Ineligibility Reason (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## 21. Appendix – eCRF

**PATIENT ELEMENTS eCRF**

**Country:**
**Center ID:**
**Patient ID:**

### DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Age:</th>
<th>[ ] years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
<td>Male [ ]</td>
</tr>
<tr>
<td></td>
<td>Female [ ]</td>
</tr>
</tbody>
</table>

**Acute intoxication:**

<table>
<thead>
<tr>
<th>Alcohol beverages (beer, wine, spirits):</th>
<th>Yes [ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No [ ]</td>
<td>Unknown [ ]</td>
</tr>
</tbody>
</table>

**Other drugs:**

<table>
<thead>
<tr>
<th>Yes [ ]</th>
<th>No [ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown [ ]</td>
<td></td>
</tr>
</tbody>
</table>

### MEDICAL HISTORY - Tick all that apply in table below

**010. Cardiovascular:**

<table>
<thead>
<tr>
<th>011. Congenital heart disease</th>
<th>087. Headache (non-migraine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>012. Arrhythmia</td>
<td>088. Migraine headaches</td>
</tr>
<tr>
<td>013. Ischemic heart disease</td>
<td>089. Previous TBI</td>
</tr>
<tr>
<td>014. Valvular heart disease</td>
<td>090. Oncologic:</td>
</tr>
<tr>
<td>015. Hypertension</td>
<td>091. Leukemia</td>
</tr>
<tr>
<td>016. Thromboembolic</td>
<td>092. Lymphoma</td>
</tr>
<tr>
<td>017. Peripheral vascular disease</td>
<td>093. Breast Cancer</td>
</tr>
</tbody>
</table>

**020. Endocrine:**

| 021. Thyroid disorder           | 095. Lung Cancer              |
| 022. IDDM                       | 096. GI Cancer                |
| 023. NIDDM                      | 097. Kidney Cancer            |

**030. Eye, Ear, Nose & Throat:**

| 031. Sinusitis                  | 098. Cancer (other)           |
| 032. Vision abnormality         | 100. Pulmonary:               |
|                                  | 101. COPD                     |
033. Hearing deficit

040. Gastrointestinal:

041. GERD

042. GI bleed

043. Inflammatory bowel disease

050. Hematologic:

051. Anemia

052. HIV positive

053. AIDS

054. Sickle cell disease

060. Hepatic:

061. Insufficiency

062. Failure

063. Hepatitis

064. Cirrhosis

070. Musculoskeletal:

071. Arthritis

080. Neurologic:

081. Cerebrovascular Accident

082. Transient ischemic attacks

084. Epilepsy: partial

085. Epilepsy: focal

086. Epilepsy: other

ADMISSION TO HOSPITAL

Diagnosis:

- Traumatic brain injury
- Spontaneous subarachnoid haemorrhage
- Intracerebral haemorrhage

Date and time of initial symptoms:

Date and time of the acute event (if different from initial symptoms):

Date and time of presentation to hospital:

Date and arrival to intensive care unit:

NEUROLOGICAL ASSESSMENT (AT ICU ADMISSION OR LAST AVAILABLE PRIOR TO ICU ADMISSION)
### Date and time:

#### Glasgow Coma Scale:

<table>
<thead>
<tr>
<th>Eyes</th>
<th>Verbal</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 []</td>
<td>2 []</td>
<td>3 []</td>
</tr>
<tr>
<td>4 []</td>
<td>5 []</td>
<td>6 []</td>
</tr>
</tbody>
</table>

#### Pupils reactivity to light (standard measurement):

- Present [ ]
- Absent [ ]

#### Dilated and unreactive pupils (standard measurement):

- Present [ ]
- Absent [ ]
- Untestable [ ]

#### Neurological Pupil index (number):

- L [ ]
- R [ ]

### INTRACRANIAL PRESSURE MONITORING

#### Intracranial pressure monitoring initiated

- Yes [ ]
- No [ ]

#### Date and Time of ICP insertion:

<table>
<thead>
<tr>
<th>DD</th>
<th>MM</th>
<th>YYYY</th>
<th>hh</th>
<th>mm</th>
</tr>
</thead>
</table>

#### Type of ICP device:

- Parenchymal [ ]
- Subdural [ ]
- Epidural [ ]
- Intraventricular [ ]

#### Date and Time of removal of ICP monitoring:

<table>
<thead>
<tr>
<th>DD</th>
<th>MM</th>
<th>YYYY</th>
<th>hh</th>
<th>mm</th>
</tr>
</thead>
</table>

#### Number of neuro-radiological investigations during first week of ICU stay:

- CT [ ]
- MRI [ ]

#### Number of neuro-surgical operations during first week of ICU stay:

- Operations [ ]

#### Additional neuromonitoring used:

- Brain tissue oxygen [ ]
- Micro-dialysis [ ]
- Spot EEG [ ]
- Continuous EEG [ ]

- Trans-cranial Doppler [ ]
- Brain ultrasound [ ]
<table>
<thead>
<tr>
<th>Option</th>
<th>Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near-Infrared</td>
<td></td>
</tr>
<tr>
<td>spectroscopy</td>
<td></td>
</tr>
<tr>
<td>Optic nerve sheath</td>
<td></td>
</tr>
<tr>
<td>diameter</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>
NPI and matched ICP daily DATA CAPTURE (Day 1 to 7)

<table>
<thead>
<tr>
<th>4-h NPI eCRF -</th>
<th>04:00</th>
<th>08:00</th>
<th>12:00</th>
<th>16:00</th>
<th>20:00</th>
<th>24:00</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPI left:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI right:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient receives continuous sedation infusion (Y/N):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient receives continuous opioid infusion (Y/N):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4-h ICP eCRF -</th>
<th>04:00</th>
<th>08:00</th>
<th>12:00</th>
<th>16:00</th>
<th>20:00</th>
<th>24:00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial pressure (mmHg):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of ICP episodes with ICP &gt;20 mmHg in the previous 4-h time interval:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max ICP recorded in the previous 4-h time interval (mmHg):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIL-4:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol given in the previous 4-h time interval (YES / NO):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertonic saline given in the previous 4-h time interval (YES / NO):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral perfusion pressure (mmHg):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PbtO₂ (mmHg) (if available):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO₂ (mmHg):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂ (mmHg):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Sodium (mmol/L):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICP 20 index over the 24 hours:</td>
<td>☐ ☐</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIL max over the 24 hours:</td>
<td>☐ ☐</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Surgery for refractory ICP (decompression, lobectomy) ☐

Orange protocol V 2.0 20Feb2020
<table>
<thead>
<tr>
<th>Effect of treatment on ICP:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>ICP reduction to normal level</td>
</tr>
<tr>
<td>Escalation to next TIL level</td>
</tr>
<tr>
<td>Surgery required</td>
</tr>
<tr>
<td>Failure to control ICP</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Specify:</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
### THERAPY INTENSITY LEVELS AND NEUROIMAGING IN THE LAST 24 HOURS

#### Table 1. Therapy Intensity Level Scale

<table>
<thead>
<tr>
<th>Item</th>
<th>Details</th>
<th>Specifics</th>
<th>Score</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positioning</td>
<td>Head elevation for ICP control</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nursed flat (180°) for CPP management</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sedation and neuromuscular blockade</td>
<td>Low dose sedation (as required for mechanical ventilation)</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Higher dose sedation for ICP control (but not aiming for burst suppression)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High dose propofol or barbiturates for ICP control (metabolic suppression)</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurovascular blockade (paralysis)</td>
<td>CSF drainage: low volume</td>
<td>&lt;120 mL/day (&lt;5 mL/h)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>CSF drainage: high volume</td>
<td>≥120 mL/day (≥5 mL/h)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CSF drainage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPP management</td>
<td>Fluid loading for maintenance of cerebral perfusion</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vasopressor therapy required for maintenance of cerebral perfusion</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilatory management(*)</td>
<td>Mild hypocapnia for ICP control, based on arterial CO2 in mm Hg</td>
<td>≥35, &lt;40</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Moderate hypocapnia for ICP control</td>
<td>≥30, &lt;35</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intensive hypocapnia for ICP control</td>
<td>&lt;30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperosmolar therapy(#)</td>
<td>Mannitol</td>
<td>≤2g/kg/24h</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Manntiol</td>
<td>&gt;2g/kg/24h</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertonic saline</td>
<td>≤0.3g/kg/24h</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertonic saline</td>
<td>&lt;0.3g/kg/24h</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Temperature control</td>
<td>Treatment of fever (T&gt;38°C or spontaneous T&lt;34.5°C)</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cooling for ICP control, ≥35°C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery for intracranial hypertension</td>
<td>Intracranial operation for progressive mass lesion, NOT scheduled on admission</td>
<td>4</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decompressive craniectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum total possible score</td>
<td></td>
<td></td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

ICP, intracranial pressure; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid.
The scheme for Therapy Intensity Level assessment, based on Maas et al., minimally adapted. Initial problems in the pilot phase that were subsequently addressed were:

(*) Conversions between kPa and mm Hg for PaCO2 were ambiguous because of “rounding up” errors. We consequently decided to base our calculations on mm Hg, which resulted in less ambiguous cutoffs.

(1) For the 4-h assessments, we used 0.53 g/kg/4h for mannitol and 0.05 g/kg/4h for hypertonic saline to assign a score value. In the pilot phase of the study, however, these cutoffs were calculated from the 24-h thresholds (inconsistently) by individual raters. In addition, because of lack of clarity in scoring instructions, some cases scored maximally in this category for the 4-h assessment, but were wrongly not scored as maximal for the 24-h assessment, because the total dose of hyperosmolar agent did not exceed thresholds when averaged over 24 h. In a revised version, we explicitly stated that if the dose of hyperosmolar agent exceeded a given threshold in any 4-h epoch, the same score should apply to the 24-h period in which that 4-h epoch was contained.

---

**Last available neuroimaging investigation**

**CT Score TBI**

Marshall CT* I □ II □ III □ IV □ V □ VI □

Midline shift □ □ □ □ mm

Basal cisterns □ Visible □ Compressed □ Completely Effaced

**CT score SAH**

Fisher CT** 1 □ 2 □ 3 □ 4 □

**CT Descriptors ICH**

Infratentorial □

Supratentori □

l □

al

< 30 ml □

≥ 30 ml □

IVH □

no IVH □

Orange protocol V 2.0 20Feb2020

<table>
<thead>
<tr>
<th>Total number of CT performed (first 7 days):</th>
<th></th>
</tr>
</thead>
</table>
### CDEs - DISCHARGE STATUS eCRF

#### DISCHARGE FROM ICU

**Date and Time of Discharge from ICU:**
DD MM YYYY hh mm

**Status on Discharge from ICU (Glasgow Outcome Score-Extended):**
- 1 – Death
- 2 – Vegetative State
- 3 – Lower Severe Disability
- 4 – Upper Severe Disability
- 5 – Lower Moderate Disability
- 6 – Upper Moderate Disability
- 7 – Lower Good Recovery
- 8 – Upper Good Recovery
- Unknown

#### DISCHARGE FROM HOSPITAL

**Date and Time of Discharge from Hospital:**
DD MM YYYY hh mm

**Discharged to:**
- Other hospital
- Rehabilitation unit
- Nursing home
- Home
- N/A Death
- Unknown
- Other

**Specify:**

**Status on Discharge from hospital (GOS-E):**
- 1 – Death
- 2 – Vegetative State
- 3 – Lower Severe Disability
- 4 – Upper Severe Disability
- 5 – Lower Moderate Disability
- 6 – Upper Moderate Disability
- 7 – Lower Good Recovery
- 8 – Upper Good Recovery
- Unknown

**Principal cause of death:**
<table>
<thead>
<tr>
<th>Condition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Head injury/initial injury</td>
<td>☐</td>
</tr>
<tr>
<td>Head injury/Secondary brain damage</td>
<td>☐</td>
</tr>
<tr>
<td>Systemic trauma</td>
<td>☐</td>
</tr>
<tr>
<td>Medical complication</td>
<td>☐</td>
</tr>
<tr>
<td>Unknown</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>☐</td>
</tr>
</tbody>
</table>

Specify ____________________________
CDEs – FOLLOW-UP AND END OF STUDY eCRF

**END OF STUDY FORM**

<table>
<thead>
<tr>
<th>Date end of study participation:</th>
<th>DD-MM-YYYY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Reason for end of study participation:</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion of study</td>
<td></td>
</tr>
<tr>
<td>Inability to obtain follow-up</td>
<td>☐</td>
</tr>
<tr>
<td>Withdrawal from study (by patient or representative)</td>
<td>☐</td>
</tr>
<tr>
<td>Decision for withdrawal of care and DNCPR</td>
<td>☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Have all the forms pertaining the study been completed:</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>☐</td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>☐</td>
</tr>
<tr>
<td>Violation study conduct</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Status at 6 months from injury (GOS-E):</th>
<th>☐ Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – Death</td>
<td></td>
</tr>
<tr>
<td>2 – Vegetative State</td>
<td></td>
</tr>
<tr>
<td>3 – Lower Severe Disability</td>
<td></td>
</tr>
<tr>
<td>4 – Upper Severe Disability</td>
<td></td>
</tr>
<tr>
<td>5 – Lower Moderate Disability</td>
<td></td>
</tr>
<tr>
<td>6 – Upper Moderate Disability</td>
<td></td>
</tr>
<tr>
<td>7 – Lower Good Recovery</td>
<td></td>
</tr>
<tr>
<td>8 – Upper Good Recovery</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Principal cause of death:</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head injury/initial injury</td>
<td>☐</td>
</tr>
<tr>
<td>Head injury/Secondary brain damage</td>
<td>☐</td>
</tr>
<tr>
<td>Systemic trauma</td>
<td>☐</td>
</tr>
<tr>
<td>Medical complication</td>
<td>☐</td>
</tr>
<tr>
<td>Unknown</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>☐</td>
</tr>
</tbody>
</table>

Specify: 

---

Orange protocol V 2.0 20Feb2020
22. Appendix 5 – Scales used in the eCRF

**Marshall CT score for Traumatic Brain Injury**

<table>
<thead>
<tr>
<th>Diffuse injury I (no visible pathology)</th>
<th>No visible intracranial pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse injury II</td>
<td>Midline shift of 0 to 5 mm</td>
</tr>
<tr>
<td></td>
<td>Basal cisterns remain visible</td>
</tr>
<tr>
<td></td>
<td>No high or mixed density lesions &gt;25 cm³</td>
</tr>
<tr>
<td>Diffuse injury III (swelling)</td>
<td>Midline shift of 0 to 5 mm</td>
</tr>
<tr>
<td></td>
<td>Basal cisterns compressed or completely effaced</td>
</tr>
<tr>
<td></td>
<td>No high or mixed density lesions &gt;25 cm³</td>
</tr>
<tr>
<td>Diffuse injury IV (shift)</td>
<td>Midline shift &gt; 5 mm</td>
</tr>
<tr>
<td></td>
<td>No high or mixed density lesions &gt;25 cm³</td>
</tr>
<tr>
<td>Evacuated mass lesion V</td>
<td>Any lesion evacuated surgically &gt;25 cm³</td>
</tr>
<tr>
<td>Non-evacuated mass lesion VI</td>
<td>High or mixed density lesions &gt;25 cm³</td>
</tr>
<tr>
<td></td>
<td>Not surgically evacuated</td>
</tr>
</tbody>
</table>

Fisher Scale for aneurysmal Subarachnoid Haemorrhage

Calculator online https://www.mdcalc.com/modified-fisher-grading-scale-subarachnoid-hemorrhage-sah

<table>
<thead>
<tr>
<th>grade 0</th>
<th>no subarachnoid (SAH) or intraventricular haemorrhage (IVH) detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>grade 1</td>
<td>focal or diffuse thin (&lt;1 mm) SAH</td>
</tr>
<tr>
<td></td>
<td>no IVH</td>
</tr>
<tr>
<td>grade 2</td>
<td>focal or diffuse (&lt;1 mm) SAH</td>
</tr>
<tr>
<td></td>
<td>IVH present</td>
</tr>
<tr>
<td>grade 3</td>
<td>thick focal or diffuse (&gt;1 mm) SAH</td>
</tr>
<tr>
<td></td>
<td>no IVH</td>
</tr>
<tr>
<td>grade 4</td>
<td>thick focal or diffuse (&gt;1 mm) SAH</td>
</tr>
<tr>
<td></td>
<td>IVH present</td>
</tr>
</tbody>
</table>
Calculation of the volume of ICH

Volume of Hemorrhage = A × B × C × Slices / Hemorrhage Shape

Calculator online at https://www.mdcalc.com/abc2-formula-intracerebral-hemorrhage-volume
**Extended GOS**

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Vegetative state</td>
<td>VS</td>
</tr>
<tr>
<td>3</td>
<td>Lower severe disability</td>
<td>SD -</td>
</tr>
<tr>
<td>4</td>
<td>Upper severe disability</td>
<td>SD +</td>
</tr>
<tr>
<td>5</td>
<td>Lower moderate disability</td>
<td>MD -</td>
</tr>
<tr>
<td>6</td>
<td>Upper moderate disability</td>
<td>MD +</td>
</tr>
<tr>
<td>7</td>
<td>Lower good recovery</td>
<td>GR -</td>
</tr>
<tr>
<td>8</td>
<td>Upper good recovery</td>
<td>GR +</td>
</tr>
</tbody>
</table>

For the evaluating the Extended Glasgow Outcome score refer to:
- [http://www.tbi-impact.org/cde/mod_templates/12_F_01_GOSE.pdf](http://www.tbi-impact.org/cde/mod_templates/12_F_01_GOSE.pdf)