



International prospective observational **Study** on **iNtrA**cranial **PreSsurE** in intensive care (**ICU**)

The SYNAPSE-ICU Study



ClinicalTrials.gov Identifier: NCT03257904

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1. Protocol Changes History

Version	Description	Date	Authors/Reviewers
V 1.0	First Draft Protocol	11/08/2017	LP/GC
V 1.1	Complete Protocol	21/08/2017	LP/GC
V 2.0	First Revised Protocol	14/09/2017	Steering Committee
V 3.1	Final Protocol	22/10/2017	Steering Committee/ESICM

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3. National Coordinators and National Societies

To be appointed

4. Summary

Title	International prospective observational Study on iNtrAcranial PreSsurE in intensive care (ICU)
Short Title	SYNAPSE-ICU
Study Design	Prospective, Observational, Cohort Study
Sponsors	University Milano Bicocca European Society of Intensive Care Medicine
Objectives	<p>The objectives of the study are:</p> <ul style="list-style-type: none"> • To evaluate the determinants (geographic area, ICU management, pathology) of practice variations in ICP monitoring in neurocritical care. • To evaluate whether the interventions (measured as Therapy Intensity Level) and investigations (additional neuromonitoring and neuroimaging) are different in acute brain injured patients with/without ICP monitoring and in non-traumatic brain injury compared to TBI. • To evaluate if having an ICP monitoring and an ICP driven therapy improves long term outcome, measured with the extended GOS.
Methods	<p>Sample Size: This international prospective observational study aims to recruit >5000 patients in coma after acute traumatic and non-traumatic brain damage admitted to >200 Intensive Care Units.</p> <p>Inclusion Criteria:</p> <ol style="list-style-type: none"> Acute brain injury (ABI) admitted to ICU following: <ul style="list-style-type: none"> • Haemorrhagic stroke, including intracerebral hematoma and subarachnoid haemorrhage, • Traumatic brain injury (penetrating and non-penetrating). Age >18 years old. Worst motor score <6 or requiring intubation and ventilation for neurological reasons/deterioration No eye opening at enrolment. <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> Acute brain injury (ABI) NOT admitted to ICU ABI not included in the inclusion criteria Age < 18 years old Motor score of the Glasgow Coma Scale on admission to ICU = 6. <p>Outcome measures: Glasgow Outcome Scale-Extended at 6 months.</p> <p>Endpoint: The primary endpoint of the study is to evaluate the determinants (geographic area, ICU management, pathology, severity) of practice variations in ICP monitoring in neurocritical care.</p>
Duration of study	<p>Screening and recruitment: 12 weeks at each centre (Aim 30 patients/centre. Ceiling to 30 patients/centre for each pathology).</p> <p>Follow-up: Outcome measures will be collected at 3-6 months.</p> <p>Duration of study: 2 years.</p>
Funding	ESICM Trial Group supported the trial with an unrestricted grant of 50,000 Euro.

5. Introduction

Intracranial pressure (ICP) monitoring is the most common neuromonitoring modality used in neurocritical care (NCCU) internationally. Its application both as a standalone monitoring or in association with other modalities (brain oxygenation, brain microdialysis, electroencephalography, transcranial Doppler ultrasound, etc.) has several indications, which rely on local, national policies and international guidelines. The Multidisciplinary Consensus Statement, promoted by ESICM with other Societies, aimed at providing guidance on Multimodality Monitoring in Neurocritical Care, including ICP [1].

However, the interpretation of data on ICP practice has limited value without some reference to the intensity of therapy directed at control of ICP [2]. The Therapy Intensity Level (TIL) may be a more sensitive measure of the severity of pathophysiology [3], and the effect on outcome of existing differences in practice is unclear.

Although the most recent Brain Trauma Foundation guidelines stressed the importance of ICP monitoring in severe traumatic brain injury [4], a living systematic review showed a compliance rate to these guidelines of 31% (range 18–83%) [5].

Furthermore, uncertainties remain around indication of monitoring in non-traumatic brain injury (acute subarachnoid haemorrhage and intracerebral hemorrhage) [6-9] as well as ICP thresholds, threshold-based treatment strategies [10-13] and their impact on outcome [14-17]. Where most of the ICP monitoring practice and guidance orbits around traumatic brain injury, ICP monitoring in non-traumatic brain injury is guided by institutional and ICU-led policies. This potentially accounts for an even larger practice-variation in this population.

6. Research questions and Objectives

6.1. Research questions

We hypothesize

- a) Clinical practice variations in ICP monitoring in neurocritical care.
- b) Difference in interventions (measured as Therapy Intensity Level, TIL 3 and 4) and investigations (additional neuromonitoring and neuroimaging) in acute brain injured patients with/without ICP monitoring and in non-traumatic brain injury compared to TBI.
- c) An association with worse outcomes in patients with the same entry criteria treated with/without ICP monitoring

6.2. Objectives

The objectives of the study are:

- a) To evaluate the determinants (geographic area, ICU management, pathology,...) of practice variations in ICP monitoring in neurocritical care.
- b) To evaluate if the interventions (measured as Therapy Intensity Level) and investigations (additional neuromonitoring and neuroimaging) are different in acute brain injured patients with/without ICP monitoring and in non-traumatic brain injury compared to TBI.
- c) To evaluate if having an ICP monitoring and an ICP driven therapy improves long term outcome, measured with the extended GOS.

7. Methods

This is a prospective, observational, international cohort study focussed at capturing:

- The aetiology of brain injury and indication ICP monitoring (ICPm) vs no-ICPm,
- The local definition of ICP threshold and incidence of high ICP,
- Threshold-based treatment strategies and measurable effects,
- NCCU resource utilization of ICPm vs no-ICPm,
- Mortality and long-term outcome measures of neurological disability.

7.1. Sample size calculation

The primary endpoint of the study is the exploration of the effect size of the variation in clinical practice around ICPm in acute brain injury patients. The hypotheses of the study are exploratory; hence a sample size calculation has not been conducted.

This international prospective observational study aims to recruit >5000 patients in coma after acute traumatic and non-traumatic brain damage admitted to > 200 Intensive Care Units (ICUs). Recruitment will last 12 weeks at each centre, aiming to enrol 30 patients/centre. For avoid an overrepresentation of some centers we ceil the data collection to 30 patients/centre for each pathology. This number of enrolled patients and ICUs reflects an adequate sample size to capture a range of variation in practice between ICUs. We aim to include also LMICs, usually not participating to these studies, in order to have a representation of the variability worldwide.

7.2. Screening

All patients admitted to the participating ICUs in coma after an acute brain damage will be screened daily, and input into a screening log (Appendix 2. Screening Log - Registry of Comatose Patients Admission).

Each ICU will recruit eligible patients for 12 consecutive weeks and collect data for each recruited patient at 8 AM and 8 PM on day 1, 3 and 7 in an expanded eCRF (Appendix 3). Both common-data elements and aetiology-specific data will be collected. Each centre will stop recruiting after 12 weeks or once 30 patients/centre for each pathology have been enrolled.

7.3. Inclusion Criteria

- Admission to ICU following acute brain injury (ABI) in:
 - Haemorrhagic stroke, including:
 - intracerebral hematoma
 - subarachnoid haemorrhage;
 - Traumatic brain injury (penetrating and non-penetrating).
 - Age >18 years old.
 - Eye Opening of the Glasgow Coma Scale = 1 on admission to ICU or neuroworsening with no Eye opening in the first 48 hrs.
- e) Motor score of the Glasgow Coma Scale on admission to ICU <6 or neuroworsening with motor score decreased to <6 in the first 48 hrs requiring intubation and ventilation for neurological reasons/deterioration

7.4. Exclusion Criteria

- Acute brain injury (ABI) not admitted to ICU.
- Other ABI (infective CSN disorders, ischemic stroke) not included in the inclusion criteria.
- Age < 18 years old.
- Eye opening on admission > 1 or Motor score of the Glasgow Coma Scale on admission to ICU = 6 without neuroworsening in the following 48 hours.

7.5. 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 3). The Patient Element eCRF data on the decision of ICP monitoring initiation will lead automatically to the subsequent pages of the eCRF (Figure 1).

7.6. ICU Admission Data

Characteristics of ICP monitoring (timeline, type of device, additional neuro-monitoring and neuroimaging characteristics) as well as the clinical indication for insertion will be documents in the eCRF-A (Appendix 3), whereas reasons for not initiating ICP monitoring, additional neuro-monitoring and neuroimaging data will be documented in the eCRF-B (Appendix 3) (flowchart in Fig.1).

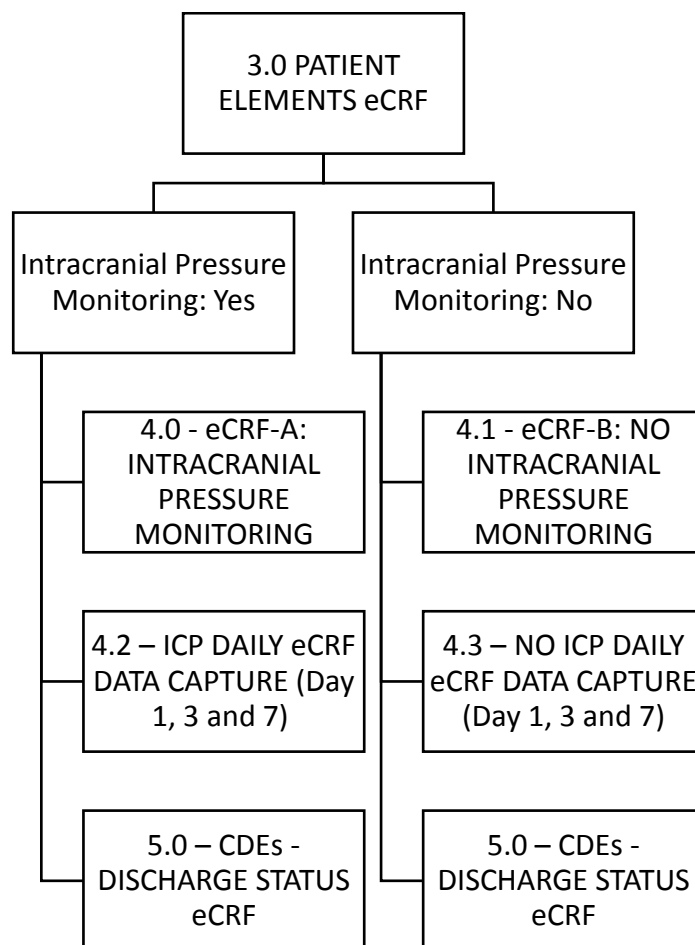


Figure 1. eCRF Flowchart

7.7. Intracranial Pressure Data and Daily eCRF

The Daily eCRF Data Capture will be completed for each pathway (ICP vs no-ICP) on day 1, 3 and 7 of ICU stay for each patient (Appendix 3). Data collected include clinical assessment (GCS, Pupils, RASS score, vital parameters, blood results) and interventions (Therapy Intensity Levels and Neuroimaging).

7.8. 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 phone structured interviews to patients and/or family members using a validated questionnaire [18].

7.9. Other complementary data

Eligible ICUs willing to participate will complete once, at the study beginning, the Centre Data Characteristics Form (Appendix 4).

7.10. Advertisement and ICU Recruitment

The study will be advertised at the annual ESICM LIVES 2017 conference and through the ESICM press/media via the Society Communication Committee. To implement the visibility of the study internationally the Steering Committee of the project will contact other societies and networks for endorsement and support (WFSICCM, LABIC, NCS, ANZICS, etc). Named National Co-ordinators will be appointed to facilitate recruitment of ICUs and identification of data-collection leads at each ICU.

7.11. Timeline

	09 17	10 17	11 17	12 17	01 18	02 18	03 18	04 18	05 18	06 18	07 18	08 18	09 18	10 18	11 18	12 18	01 19	02 19	03 19	04 19	05 19	06 19	07 19	08 19	09 19	
Protocol finalization	█																									
Presentation at LIVES 2017	█																									
Ethical submission		█	█	█	█																					
eCRF development		█	█	█	█																					
Centers recruitment		█	█	█	█																					
Patient enrolment						█	█	█																		
Follow-up													█	█	█											
Data completion															█	█										
Analysis																	█	█	█	█	█					
Manuscript preparation																					█	█	█	█	█	█
Presentation of results																										█

The planned enrolment phase might be postponed (till summer 2018) accordingly to the time required by the centers to obtain local Institutional Review Board approvals.

8. Endorsement, Funding & Methodological Support

The SYNAPSE-ICU study has been endorsed by the European Society of Intensive Care Medicine (ESICM) on the 31st January 2017 and has been included in the ESICM Trials Group Portfolio on the 11th August 2017. The study is partly funded by an ESICM grant (ESICM Trials Group).

9. Potential Risks and Benefits

9.1. Risks

The study SYNAPSE-ICU 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.

9.2. Benefits

The patients enrolled in the study will not benefit directly from the research. The potential benefit of the study consists in improving knowledge for a better medical management 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 Steering Committee. 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 National Coordinators/Local PIs 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 Steering Committee agrees 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 (eCRF, Appendix 2). 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.

Centres not able to complete an electronic CRF will be given the possibility to complete a paper version. These records will be shipped to the CI via signed post and then entered into the eCRF at Università Milano Bicocca by the local research staff.

12. Statistical methods

Descriptive statistics will be used to summarise the database characteristics through exploratory data analysis methods, which will represent data visually and in tables for reporting and publication purpose.

Traditional regression analyses will serve as inferential statistics methods. Due to the large dimensionality of data collected a dedicated statistical team will also use advanced statistical analysis including random effect models to quantify between-ICU differences, clinical data partitioning algorithms and machine-learning classifiers. The effect of ICP monitoring and therapy will be analysed both at patient and ICU level.

Common-data elements will be analysed for all patients in a single statistical approach, whereas aetiology-specific data may require sub-studies and dedicated processing.

13. Source documents and access to source data/documents

13.1. Access to data

The 'SYNAPSE-ICU investigators' own the data collectively. The SYNAPSE-ICU investigators consist of:

- The Steering and Executive Committees,
- The National coordinators and

- The individual ICU Site coordinators.

Individual 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. National coordinators will be given access upon request to their country specific data. By entering data into the SYNAPSE-ICU database, each centre agrees that the SYNAPSE-ICU Steering and Executive committees can use these data for scientific purposes. Any requests for the use of the data will be made to the SYNAPSE-ICU Steering Committee. The SYNAPSE-ICU investigators will have priority in requests to use the data set for subsequent studies.

13.2. 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.

13.3. 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 de-identified and anonymized at input into the eCRF by the local centres/PIs. 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. Centres not able to complete an electronic CRF will be given the possibility to complete a paper version. These records will be shipped to the CI via signed post and then entered into the eCRF at University Milano Bicocca by the local research staff.

14. Ethics/Protection of Human rights

14.1. Ethical standards

The PI and Steering Committee will ensure that this study is conducted in full conformity with the Declaration of Helsinki and Good Clinical Practices.

14.2. Ethics committee

Each NC/PI will notify the relevant ethics committee, in compliance with the local legislation and rules. The national coordinators will facilitate this process. 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 SC before the changes are implemented to the study.

14.3. 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 10.4. 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.

14.4. 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

15.1. Data collection and management responsibilities

The data resides at the PI's 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.

15.2. Study record retention

All standard practices with regards to the locked storage, password-protected backup, and security of this data will be observed both locally and centrally (ESICM). 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. Upon request, ESICM shall provide the individual country regulatory authorities with information required to enable them to verify compliance with these data security measures.

16. Responsibilities

16.1. Chief investigator and Steering Committee

The role and responsibilities of the Chief Investigator 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.
- to assist the monitoring committee in communicating with sites regarding data queries.
- is the main responsible of the collected data, statistical analysis, communication and publications.

16.2. Country coordinators

The role and responsibilities of the country coordinators are:

- to liaise with National Intensive Care Societies and advertise the study in the individual countries and identify participating sites and local PIs in their country.
- 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.
- to ensure good communication with the participating sites in their country, including monitoring and encouraging to achieve optimal recruitment and follow-up during the period of the study.
- to assist the monitoring committee in communicating with sites regarding data queries.

16.3. Site investigators

For each participating ICU, one local investigator should be 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

17.1. Data sharing policy

Any requests for the use of the data will be made to the SYNAPSE-ICU Steering Committee, and decisions will be made in relation to these requests. The SYNAPSE-ICU investigators will have priority in requests to use the data set for subsequent studies.

17.2. Publication and Authorship

Data will be made available to ESICM members and to the scientific community by means of abstract submitted to the ESICM annual conference 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 4 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.

A writing committee, composed by some Steering Committee members, will draft the work and the SC members will be authors of the manuscript. National coordinators will be authors if they will fulfil the ICMJE criteria and if they will promote the enrolment of at least 500 ABI patients in their country. All the participant centres will be granted in the group authorship, "SYNAPSE-ICU". 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. The ESICM support will be acknowledged in each publication generated from the study.

18. Expected impact of the study

The investigators expect to obtain data of >5000 ABI patients admitted to ICU. The expected recruitment counts for ~ 50% acute traumatic brain injury and ~ 50% of acute non-traumatic brain injury (acute subarachnoid haemorrhage and intracerebral haemorrhage).

These data will allow a detailed description of patient's characteristics, management strategies resource use and correlation with clinical outcomes. In particular, the study will provide insights in relation to ICP monitoring and treatment, practice

variation in neurointensive care units around the world, differences in the management of TBI and non-TBI patients including treatment thresholds, therapeutic strategies and their potential association with outcome.

19. References

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20. Appendix 1 - List of Abbreviations

AIDS – Acquired Immune Deficiency Syndrome

CNS – Central Nervous System

COPD – Chronic Obstructive Pulmonary Disease

CSF – Cerebrospinal Fluid

CT – Computerised Tomography

DBP – Diastolic Blood Pressure

DNCPR – Do Not Cardio-Pulmonary Resuscitate

eCRF – electronic Case Report Form

ESICM – European Society of Intensive Care Medicine

GCS – Glasgow Coma Scale

GI – Gastro-Intestinal

GORD – Gastro-Oesophageal Reflux Disease

HDU – High Dependency Unit

HIV – Human Immunodeficiency Virus

ICH – Intracerebral Haemorrhage

ICP – Intracranial Pressure

ICPm – Intracranial Pressure monitoring

ICU- Intensive Care Unit

IDDM – Insulin Dependent Diabetes Mellitus

IIU – Intermediate Intensity Unit

IVH – Intraventricular Haemorrhage

NIDDM – Non-Insulin Dependent Diabetes Mellitus

PaCO₂ – Arterial Partial Pressure of Carbon Dioxide

PaO₂ – Arterial Partial Pressure of Oxygen

SAH – Subarachnoid Haemorrhage

SBP – Systolic Blood Pressure

TBI – Traumatic Brain Injury

TIL – Therapy Intensity Level

UTI – Urinary Tract Infection

21. Appendix 2 – Screening Log

Tool Summary Sheet

Tool: Site Screening and Enrolment 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, clinical monitor

Details: This log should provide a comprehensive list of all subjects who were screened for eligibility if the information is not maintained electronically.

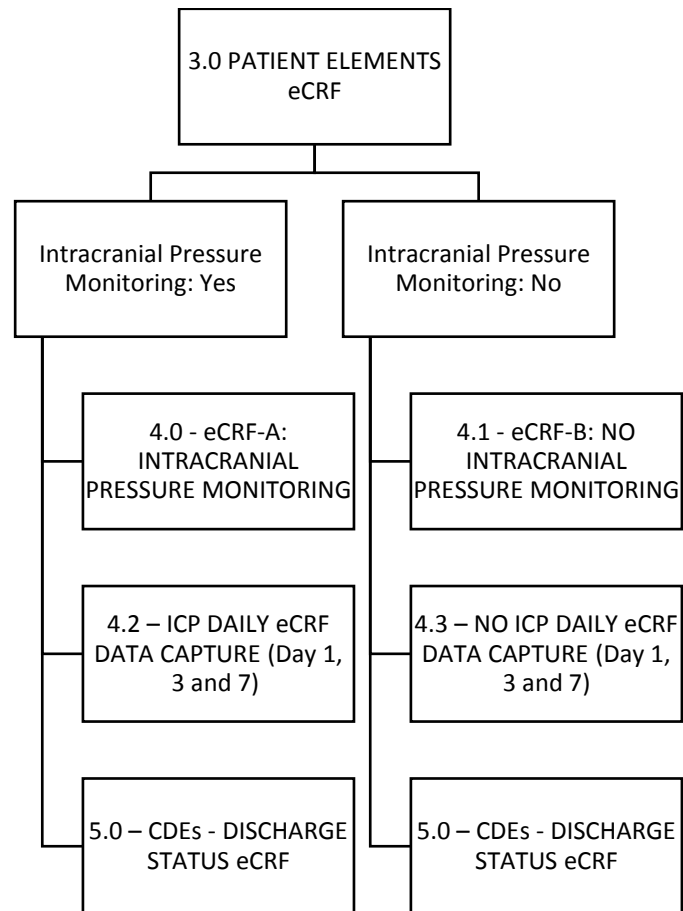
- Best Practice Recommendations:**
- Record subjects as they are consented, to ensure completeness and accuracy of the data.
 - Include all subjects who were consented and screened, including screen failures.
 - This log should contain no identifying information. Subjects may be tracked separately on 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.

Site Screening and Enrolment Log (Registry of Comatose Patients Admission)

Investigator Name:	Protocol:	Site Number:
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Subject ID	Date of Consent	Version of Consent	Date Screened	Eligible for Enrolment?	Ineligibility Reason (if applicable)

22. Appendix 3 – eCRF



22.1. PATIENT ELEMENTS eCRF

Country:

Center ID:

Patient ID:

DEMOGRAPHICS

Age: years

Sex: Male Female

Acute intoxication:

Alcohol beverages (beer, wine, spirits): Yes

No

Unknown

Other drugs: Yes

No

Unknown

MEDICAL HISTORY - Tick all that apply in table below

010. Cardiovascular:

011. Congenital heart disease 087. Headache (non-migraine)

012. Arrhythmia 088. Migraine headaches

013. Ischemic heart disease 089. Previous TBI

014. Valvular heart disease **090. Oncologic:**

015. Hypertension 091. Leukemia

016. Thromboembolic 092. Lymphoma

017. Peripheral vascular disease 093. Breast Cancer

020. Endocrine: 094. Prostate Cancer

021. Thyroid disorder 095. Lung Cancer

022. IDDM 096. GI Cancer

023. NIDDM 097. Kidney Cancer

030. Eye, Ear, Nose & Throat: 098. Cancer (other)

031. Sinusitis **100. Pulmonary:**

032. Vision abnormality 101. COPD

033. Hearing deficit 102. Asthma

040. Gastrointestinal: 103. Pneumonia

041. GERD 104. Tuberculosis

042. GI bleed **110. Psychiatric:**

043. Inflammatory bowel disease 111. Anxiety

050. Hematologic: 112. Depression

051. Anemia 113. Sleep disorder

052. HIV positive 114. Schizophrenia

053. AIDS 115. Other psychiatric disorder

054. Sickle cell disease **120. Renal:**

060. Hepatic: 121. Insufficiency

061. Insufficiency 122. Failure

062. Failure 123. Chronic UTI's

063. Hepatitis **130. Social history:**

064. Cirrhosis 131. Tobacco use

070. Musculoskeletal: 132. Alcohol use

071. Arthritis 133. Drug use

080. Neurologic: **140. Developmental history:**

081. Cerebrovascular Accident 141. Learning disabilities

082. Transient Ischemic Attacks 142. Attention deficit/hyperactivity disorder

084. Epilepsy: partial

085. Epilepsy: focal

086. Epilepsy: other

ADMISSION TO HOSPITAL

Diagnosis:	
Traumatic Brain Injury	<input type="checkbox"/>
Spontaneous Subarachnoid Haemorrhage	<input type="checkbox"/>
Intracerebral haemorrhage	<input type="checkbox"/>

Date and time of initial symptoms:	DD <input type="checkbox"/> <input type="checkbox"/> MM <input type="checkbox"/> <input type="checkbox"/> YYYY <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	hh <input type="checkbox"/> <input type="checkbox"/> mm <input type="checkbox"/> <input type="checkbox"/>
Date and time of the acute event (if different from initial symptoms):	DD <input type="checkbox"/> <input type="checkbox"/> MM <input type="checkbox"/> <input type="checkbox"/> YYYY <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	hh <input type="checkbox"/> <input type="checkbox"/> mm <input type="checkbox"/> <input type="checkbox"/>
Date and time of presentation to hospital:	DD <input type="checkbox"/> <input type="checkbox"/> MM <input type="checkbox"/> <input type="checkbox"/> YYYY <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	hh <input type="checkbox"/> <input type="checkbox"/> mm <input type="checkbox"/> <input type="checkbox"/>
Date and arrival to Intensive Care Unit:	DD <input type="checkbox"/> <input type="checkbox"/> MM <input type="checkbox"/> <input type="checkbox"/> YYYY <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	hh <input type="checkbox"/> <input type="checkbox"/> mm <input type="checkbox"/> <input type="checkbox"/>

NEUROLOGICAL ASSESSMENT (AT ICU ADMISSION OR LAST AVAILABLE PRIOR TO ICU ADMISSION)

Glasgow Coma Scale:	
Eyes	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> U <input type="checkbox"/>
Verbal	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> T <input type="checkbox"/>
Motor	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> U <input type="checkbox"/>
Pupils reactivity to light	Present <input type="checkbox"/> Absent <input type="checkbox"/>
Dilated and unreactive pupils	Present <input type="checkbox"/> Absent <input type="checkbox"/>
	Untestable <input type="checkbox"/>

INTRACRANIAL PRESSURE MONITORING

Intracranial pressure monitoring planned	Yes	<input type="checkbox"/>	NO	<input type="checkbox"/>
Intracranial pressure monitoring initiated	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>

22.2. eCRF-A: INTRACRANIAL PRESSURE MONITORING

INTRACRANIAL PRESSURE MONITORING

Reason of ICP monitoring:

- | | |
|------------------------------------|-------------------------------|
| Clinical Indication (Low GCS/Coma) | <input type="checkbox"/> |
| Radiology/Anatomy of injury | <input type="checkbox"/> |
| Local Policy | <input type="checkbox"/> |
| Neuroworsening* | <input type="checkbox"/> |
| Other | Specify: <input type="text"/> |

*Neuroworsening defined as one or more of the following:

- a spontaneous decrease in the GCS motor score of 2 points or more compared with the previous examination
- a new loss of pupillary reactivity, development of pupillary asymmetry ≥ 2 mm
- deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention

Date and Time of ICP insertion: DD MM YYYY hh mm

Inserted in:

- | | |
|---------------------|--------------------------|
| Intensive Care Unit | <input type="checkbox"/> |
| Operating Room | <input type="checkbox"/> |

Inserted by:

- | | |
|------------------|--------------------------|
| Neurosurgeon | <input type="checkbox"/> |
| Neurointensivist | <input type="checkbox"/> |
| Other | <input type="checkbox"/> |

Specify:

Type of ICP device:

- | | |
|------------------|--------------------------|
| Parenchymal | <input type="checkbox"/> |
| Subdural | <input type="checkbox"/> |
| Epidural | <input type="checkbox"/> |
| Intraventricular | <input type="checkbox"/> |

Platelets value before insertion: x 10³/microliter

INR value before insertion:

Antimicrobial prophylaxis: Yes No

Date and Time of ICP change: DD MM YYYY hh mm

Date and Time of removal of ICP monitoring: DD MM YYYY hh mm

Reason for stopping:

- | | |
|----------------------------------|--------------------------|
| Normal ICP | <input type="checkbox"/> |
| Clinically improved | <input type="checkbox"/> |
| Monitor/Catheter failure | <input type="checkbox"/> |
| Patient considered unsalvageable | <input type="checkbox"/> |
| Patient died | <input type="checkbox"/> |

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 | <input type="checkbox"/> |
| Micro-dialysis | <input type="checkbox"/> |
| Spot EEG | <input type="checkbox"/> |
| Continuous EEG | <input type="checkbox"/> |
| Trans-cranial Doppler | <input type="checkbox"/> |
| Brain ultrasound | <input type="checkbox"/> |

Near-Infrared spectroscopy

Optic nerve sheath diameter

Pupillometry

Other Specify:

Neuroworsening* Yes No

*Neuroworsening defined as one or more of the following:

- a spontaneous decrease in the GCS motor score of 2 points or more compared with the previous examination
- a new loss of pupillary reactivity, development of pupillary asymmetry ≥ 2 mm

deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention

22.3. eCRF-B: NO INTRACRANIAL PRESSURE MONITORING

Reason for no ICP monitoring:

Clinical Indication	<input type="checkbox"/>
Radiology/Anatomy of injury	<input type="checkbox"/>
Patient considered unsalvageable	<input type="checkbox"/>
Coagulopathy	<input type="checkbox"/>
Monitor/ICP catheter not available	<input type="checkbox"/>
No policy of ICP measurement	
Other	Specify: <input type="text"/>

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:

Additional neuromonitoring used:

Brain tissue oxygen	<input type="checkbox"/>
Micro-dialysis	<input type="checkbox"/>
Spot EEG	<input type="checkbox"/>
Continuous EEG	<input type="checkbox"/>
Trans-cranial Doppler	<input type="checkbox"/>
Brain ultrasound	<input type="checkbox"/>
Near-Infrared spectroscopy	<input type="checkbox"/>
Optic nerve sheath diameter	<input type="checkbox"/>
Pupillometry	<input type="checkbox"/>
Other	Specify: <input type="text"/>

Neuroworsening* Yes No

*Neuroworsening defined as one or more of the following:

- a spontaneous decrease in the GCS motor score of 2 points or more compared with the previous examination
- a new loss of pupillary reactivity, development of pupillary asymmetry $\geq 2\text{mm}$

deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention

22.4. ICP DAILY eCRF DATA CAPTURE (Day 1, 3 and 7)

DAILY eCRF - ICP

8 AM

Intracranial pressure: mmHg
 Max ICP recorded in the previous 24 hrs mmHg
 Number of Sedation hold/Wake-up tests: Wake-up Tests

Best GCS recorded:

Eyes 1 2 3 4 U

Verbal 1 2 3 4 5 T

Motor 1 2 3 4 5 6 U

Pupil reactivity to light Present Absent

Pupils dilated not reactive Present Absent

Untestable Untestable

Patient not evaluated

Richmond Agitation-Sedation Scale

+4 Combative

+3 Very Agitated

+2 Agitated

+1 Restless

0 Alert and Calm

-1 Drowsy

-2 Light Sedation

-3 Moderate Sedation

-4 Deep Sedation

-5 Unarousable

Blood Pressure: SBP / DBP mmHg

Heart rate: bpm

Core Temperature: C

PaO₂: mmHg

PaCO₂: mmHg

Blood glucose: mg/dl

Serum Sodium: mmol/L

Number of ICP spikes >20 mmHg during the last 24h that required treatment:

THERAPY INTENSITY LEVELS AND NEUROIMAGING IN THE LAST 24 HOURS

TIL 0 - No specific ICP directed therapy

TIL 1 – basic ICU care

Sedation for ventilator/endotracheal tube tolerance

Volume/vasopressors for non-CNS cause (e.g. sepsis, myocardial injury)

Head up positioning (ventilator bundle)

Normocapnia (PaCO₂ ≥ 40mmHg)

TIL 2 – Mild

Higher levels of sedation

Vasopressors/volume for CPP support

Low dose osmotic therapy

Mild hypocapnia (PaCO₂ 4.6-5.3 kPa; 35-40 mmHg)

CSF drainage < 120 ml/day (<5 ml/hour)

TIL 3 – Moderate

Higher doses of osmotic therapy

Moderate hypocapnia (PaCO₂ 4.0-4.5 kPa; 30-35 mmHg)

Mild hypothermia (> 35°C)

CSF drainage ≥ 120 ml/day (>5 ml/hour)

TIL 4 – Extreme

Profound hypocapnia (PaCO₂ < 4.0 kPa; < 30 mmHg)

Hypothermia < 35 °C

	Metabolic suppression for control of ICP	<input type="checkbox"/>
	Surgery for refractory ICP (decompression, lobectomy)	<input type="checkbox"/>
Effect of treatment on ICP:		
	ICP reduction to normal level	<input type="checkbox"/>
	Escalation to next TIL level	<input type="checkbox"/>
	Surgery required	<input type="checkbox"/>
	Failure to control ICP	<input type="checkbox"/>
	Other	<input type="checkbox"/>
	Specify: <input type="text"/>	
Last available neuroimaging investigation		
CT Score TBI	Marshall CT* I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV <input type="checkbox"/> V <input type="checkbox"/> VI <input type="checkbox"/>	
	Midline shift <input type="text"/> mm	
	Basal cisterns <input type="checkbox"/> Visible <input type="checkbox"/> Compressed <input type="checkbox"/> Completely Effaced	
CT score SAH	Fisher CT** 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/>	
CT Descriptors ICH		
	Infratentorial <input type="checkbox"/>	Supratentorial <input type="checkbox"/>
	< 30 ml <input type="checkbox"/>	≥ 30 ml <input type="checkbox"/>
	IVH <input type="checkbox"/>	no IVH <input type="checkbox"/>

22.5. NO ICP DAILY eCRF DATA CAPTURE (Day 1, 3 and 7)

DAILY eCRF – no ICP

8 AM

Number of Sedation hold/Wake-up tests:	□□□ Wake-up Tests	
Number of Sedation hold/Wake-up tests:	□□□ Wake-up Tests	
GCS:		
	Eyes	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> U <input type="checkbox"/>
	Verbal	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> T <input type="checkbox"/>
	Motor	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> U <input type="checkbox"/>
Pupils reactivity to light	Present <input type="checkbox"/>	Absent <input type="checkbox"/>
Pupils dilated not reactive	Present <input type="checkbox"/>	Absent <input type="checkbox"/>
	Untestable <input type="checkbox"/>	Untestable <input type="checkbox"/>
	Patient not evaluated <input type="checkbox"/>	
Richmond Agitation-Sedation Scale		
	+4 Combative	<input type="checkbox"/>
	+3 Very Agitated	<input type="checkbox"/>
	+2 Agitated	<input type="checkbox"/>
	+1 Restless	<input type="checkbox"/>
	0 Alert and Calm	<input type="checkbox"/>
	-1 Drowsy	<input type="checkbox"/>
	-2 Light Sedation	<input type="checkbox"/>
	-3 Moderate Sedation	<input type="checkbox"/>
	-4 Deep Sedation	<input type="checkbox"/>
	-5 Unarousable	<input type="checkbox"/>
Blood Pressure:	SBP □□□ / DBP □□□ mmHg	
Heart rate:	□□□ bpm	
Core Temperature:	□□.□ C	
PaO ₂ :	□□□ mmHg	
PaCO ₂ :	□□□ mmHg	
Blood glucose:	□□□.□□ mg/dl	
Serum Sodium:	□□□ mmol/L	
High ICP suspected in the previous 24 hrs	Present <input type="checkbox"/>	Absent <input type="checkbox"/>

THERAPY INTENSITY LEVELS AND NEUROIMAGING IN THE LAST 24 HOURS

TIL 0 - No specific ICP directed therapy	<input type="checkbox"/>
TIL 1 – basic ICU care	<input type="checkbox"/>
	Sedation for ventilator/endotracheal tube tolerance <input type="checkbox"/>
	Volume/vasopressors for non-CNS cause (e.g. sepsis, myocardial injury) <input type="checkbox"/>
	Head up positioning (ventilator bundle) <input type="checkbox"/>
	Normocapnia (PaCO ₂ ≥ 40mmHg) <input type="checkbox"/>
TIL 2 – Mild	<input type="checkbox"/>
	Higher levels of sedation <input type="checkbox"/>
	Vasopressors/volume for CPP support <input type="checkbox"/>
	Low dose osmotic therapy <input type="checkbox"/>
	Mild hypocapnia (PaCO ₂ 4.6-5.3 kPa; 35-40 mmHg) <input type="checkbox"/>
TIL 3 – Moderate	<input type="checkbox"/>
	Higher doses of osmotic therapy <input type="checkbox"/>
	Moderate hypocapnia (PaCO ₂ 4.0-4.5 kPa; 30-35 mmHg) <input type="checkbox"/>
	Mild hypothermia (> 35°C) <input type="checkbox"/>
TIL 4 – Extreme	<input type="checkbox"/>
	Profound hypocapnia (PaCO ₂ < 4.0 kPa; < 30 mmHg) <input type="checkbox"/>
	Hypothermia < 35 °C <input type="checkbox"/>
	Metabolic suppression for control of ICP <input type="checkbox"/>
	Surgery decompression, lobectomy <input type="checkbox"/>
Effect of treatment on Clinical assessment:	
	Neurological improvement <input type="checkbox"/>

Escalation to next TIL level	<input type="checkbox"/>
Surgery required	<input type="checkbox"/>
Worsening neuroimaging	<input type="checkbox"/>
Other	<input type="checkbox"/>
Specify: <input type="text"/>	
Last available neuroimaging investigation	
CT Score TBI	Marshall CT* <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV <input type="checkbox"/> V <input type="checkbox"/> VI <input type="checkbox"/>
	Midline shift <input type="text"/> mm
	Basal cisterns <input type="checkbox"/> Visible <input type="checkbox"/> Compressed <input type="checkbox"/> Completely Effaced
CT score SAH	Fisher CT** <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/>
CT Descriptors ICH	
Infratentorial	<input type="checkbox"/>
Supratentorial	<input type="checkbox"/>
< 30 ml	<input type="checkbox"/>
≥ 30 ml	<input type="checkbox"/>
IVH	<input type="checkbox"/>
no IVH	<input type="checkbox"/>

22.6. CDEs - DISCHARGE STATUS eCRF

DISCHARGE FROM ICU

Date and Time of Discharge from ICU:	DD <input type="text"/> <input type="text"/>	MM <input type="text"/> <input type="text"/>	YYYY <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	hh <input type="text"/> <input type="text"/>	mm <input type="text"/> <input type="text"/>
Status on Discharge from ICU (Glasgow Outcome Score-Extended):					
1 – Death					<input type="checkbox"/>
2 – Vegetative State					<input type="checkbox"/>
3 – Lower Severe Disability					<input type="checkbox"/>
4 – Upper Severe Disability					<input type="checkbox"/>
5 – Lower Moderate Disability					<input type="checkbox"/>
6- Upper Moderate Disability					<input type="checkbox"/>
7 – Lower Good Recovery					<input type="checkbox"/>
8 – Upper Good Recovery					<input type="checkbox"/>
Unknown					<input type="checkbox"/>

DISCHARGE FROM HOSPITAL

Date and Time of Discharge from hospital:	DD <input type="text"/> <input type="text"/>	MM <input type="text"/> <input type="text"/>	YYYY <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	hh <input type="text"/> <input type="text"/>	mm <input type="text"/> <input type="text"/>
Discharged to:					
Other hospital					<input type="checkbox"/>
Rehabilitation unit					<input type="checkbox"/>
Nursing home					<input type="checkbox"/>
Home					<input type="checkbox"/>
N/A Death					<input type="checkbox"/>
Unknown					<input type="checkbox"/>
Other					<input type="checkbox"/>

Specify:

Status on Discharge from hospital (GOS-E):					
1 – Death					<input type="checkbox"/>
2 – Vegetative State					<input type="checkbox"/>
3 – Lower Severe Disability					<input type="checkbox"/>
4 – Upper Severe Disability					<input type="checkbox"/>
5 – Lower Moderate Disability					<input type="checkbox"/>
6- Upper Moderate Disability					<input type="checkbox"/>
7 – Lower Good Recovery					<input type="checkbox"/>
8 – Upper Good Recovery					<input type="checkbox"/>
Unknown					<input type="checkbox"/>

Principal cause of death:					
Head injury/initial injury					<input type="checkbox"/>
Head injury/Secondary brain damage					<input type="checkbox"/>
Systemic trauma					<input type="checkbox"/>
Medical complication					<input type="checkbox"/>
Unknown					<input type="checkbox"/>
Other					<input type="checkbox"/>

Specify

22.7. CDEs – FOLLOW-UP AND END OF STUDY eCRF

END OF STUDY FORM

Date end of study participation:	DD	MM	YYYY	<input type="checkbox"/>
Reason for end of study participation:				
Completion of study				<input type="checkbox"/>
Inability to obtain follow-up				<input type="checkbox"/>
Withdrawal from study (by patient or representative)				<input type="checkbox"/>
Decision for withdrawal of care and DNCPR				<input type="checkbox"/>
Have all the forms pertaining the study been completed:				
Yes				<input type="checkbox"/>
No				<input type="checkbox"/>
Consent withdrawn				<input type="checkbox"/>
Violation study conduct				<input type="checkbox"/>
Other				<input type="checkbox"/>
Status at 6 months from injury (GOS-E):				
1 – Death				<input type="checkbox"/>
2 – Vegetative State				<input type="checkbox"/>
3 – Lower Severe Disability				<input type="checkbox"/>
4 – Upper Severe Disability				<input type="checkbox"/>
5 – Lower Moderate Disability				<input type="checkbox"/>
6- Upper Moderate Disability				<input type="checkbox"/>
7 – Lower Good Recovery				<input type="checkbox"/>
8 – Upper Good Recovery				<input type="checkbox"/>
Unknown				<input type="checkbox"/>
Principal cause of death:				
Head injury/initial injury				<input type="checkbox"/>
Head injury/Secondary brain damage				<input type="checkbox"/>
Systemic trauma				<input type="checkbox"/>
Medical complication				<input type="checkbox"/>
Unknown				<input type="checkbox"/>
Other				<input type="checkbox"/>
	Specify <input type="checkbox"/>			

23. Appendix 4 – Centre Data Characteristics Form

CENTRE DATA CHARACTERISTICS FORM

(To be completed as a one-off form by each participating centre)

REGISTRATION INFORMATION

Name of institution:	<input type="text"/>		
City:	<input type="text"/>		
Country:	<input type="text"/>		
Contact person:	<input type="text"/>		
Contact e-mail address:	<input type="text"/> @ <input type="text"/>		
Type of institution:			
	Academic/Teaching Hospital	<input type="checkbox"/>	
	Non-Teaching Hospital	<input type="checkbox"/>	
	Private non-academic	<input type="checkbox"/>	
	Public non-academic	<input type="checkbox"/>	
	District Hospital	<input type="checkbox"/>	
	Other	<input type="checkbox"/>	
Number of beds in your institution:			
	<250	<input type="checkbox"/>	
	250-500	<input type="checkbox"/>	
	500-750	<input type="checkbox"/>	
	750-1000	<input type="checkbox"/>	
	>1000	<input type="checkbox"/>	
Catchment area population:			
	<100.000	<input type="checkbox"/>	
	100.000-250.000	<input type="checkbox"/>	
	250.000-500.000	<input type="checkbox"/>	
	500.000-750.000	<input type="checkbox"/>	
	750.000-1.000.000	<input type="checkbox"/>	
	>1.000.000	<input type="checkbox"/>	
Neurocritical care patients are generally admitted to:			
	Specialist Neurocritical care unit	<input type="checkbox"/>	
	Mixed General-Neurocritical care unit	<input type="checkbox"/>	
	Medical ICU	<input type="checkbox"/>	
	Surgical ICU	<input type="checkbox"/>	
	Other	<input type="checkbox"/>	
Number of total ICU beds in your institution:	<input type="text"/>		beds
Number of Neurocritical care unit beds:	<input type="text"/>		beds
Number of neurocritical care patients admitted to ICU in 2016:	<input type="text"/>		patients
Medical staffing of Neurocritical care unit/ICU admitting neurocritical care patients:			
	Neurologist Intensivist	<input type="checkbox"/>	
	Anaesthetist Intensivist	<input type="checkbox"/>	
	Neurosurgeon Intensivist	<input type="checkbox"/>	
	General/Respiratory Med. Intensivist	<input type="checkbox"/>	
	Other	<input type="checkbox"/>	
Medical Staff present 24/7:			
	Yes	<input type="checkbox"/>	
		Qualified specialist	<input type="checkbox"/>
		Fellow	<input type="checkbox"/>
		Trainee	<input type="checkbox"/>
		Specialist nurse	<input type="checkbox"/>
		Telepresence	<input type="checkbox"/>
	No	<input type="checkbox"/>	
	Other	<input type="checkbox"/>	
Nurse:Patient ratio for ICU patients:			
	1:1	<input type="checkbox"/>	
	1:2	<input type="checkbox"/>	

1:3	<input type="checkbox"/>
Other	<input type="checkbox"/>
Nurse:Patient ratio for IIU/HDU patients:	
1:1	<input type="checkbox"/>
1:2	<input type="checkbox"/>
1:3	<input type="checkbox"/>
Other	<input type="checkbox"/>

ICP TREATMENT THRESHOLD

What is your high ICP threshold for treatment in TBI?	<input type="text"/> mmHg	for	<input type="text"/> hh:mm
What is your high ICP threshold for treatment in SAH?	<input type="text"/> mmHg	for	<input type="text"/> hh:mm
What is your high ICP threshold for treatment in ICH?	<input type="text"/> mmHg	for	<input type="text"/> hh:mm
Do you have an ICP management protocol/policy in your institution/ICU?	YES		NO
For TBI	<input type="checkbox"/>		<input type="checkbox"/>
For SAH	<input type="checkbox"/>		<input type="checkbox"/>
For ICH	<input type="checkbox"/>		<input type="checkbox"/>
MAP zeroing	<input type="checkbox"/> At Right Atrium level		<input type="checkbox"/> At Ear level

SOURCE OF PATIENTS' DATA

Electronic medical record	<input type="checkbox"/>
Paper medical notes	<input type="checkbox"/>
Other	<input type="checkbox"/>

Specify

24. Appendix 5 – Scales used in the eCRF

Richmond Agitation-Sedation Scale

Score	Term	Description
+4	<input type="checkbox"/> Combative	Overtly combative or violent; immediate danger to staff
+3	<input type="checkbox"/> Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour toward staff
+2	<input type="checkbox"/> Agitated	Frequent non-purposeful movement or patient–ventilator dys-synchrony
+1	<input type="checkbox"/> Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	<input type="checkbox"/> Alert and calm	Spontaneously pays attention to caregiver
-1	<input type="checkbox"/> Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	<input type="checkbox"/> Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	<input type="checkbox"/> Moderate sedation	Any movement (but no eye contact) to voice
-4	<input type="checkbox"/> Deep sedation	No response to voice, but any movement to physical stimulation
-5	<input type="checkbox"/> Unarousable	No response to voice or physical stimulation

Marshall CT score for Traumatic Brain Injury

Diffuse injury I (no visible pathology)	No visible intracranial pathology
Diffuse injury II	Midline shift of 0 to 5 mm Basal cisterns remain visible No high or mixed density lesions >25 cm ³
Diffuse injury III (swelling)	Midline shift of 0 to 5 mm Basal cisterns compressed or completely effaced No high or mixed density lesions >25 cm ³
Diffuse injury IV (shift)	Midline shift > 5mm No high or mixed density lesions >25 cm ³
Evacuated mass lesion V	Any lesion evacuated surgically >25 cm ³
Non-evacuated mass lesion VI	High or mixed density lesions >25 cm ³ Not surgically evacuated

Fisher Scale for aneurysmal Subarachnoid Haemorrhage

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

grade 0	no subarachnoid (SAH) or intraventricular haemorrhage (IVH) detected
grade 1	focal or diffuse thin (<1 mm) SAH no IVH
grade 2	focal or diffuse (<1 mm) SAH IVH present
grade 3	thick focal or diffuse (>1 mm) SAH no IVH
grade 4	thick focal or diffuse (>1 mm) SAH IVH present

Calculation of the volume of ICH

$$\text{Volume of Hemorrhage} = A \times B \times C \times \text{Slices} / \text{Hemorrhage Shape}$$

Calculator online at <https://www.mdcalc.com/abc2-formula-intracerebral-hemorrhage-volume>

Extended GOS

1	Death	D
2	Vegetative state	VS
3	Lower severe disability	SD -
4	Upper severe disability	SD +
5	Lower moderate disability	MD -
6	Upper moderate disability	MD +
7	Lower good recovery	GR -
8	Upper good recovery	GR +

For the evaluating the Extended Glasgow Outcome score refer to:

- http://www.tbi-impact.org/cde/mod_templates/12_F_01_GOSE.pdf
- Wilson JTL, Pettigrew LEL, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: Guidelines for Their Use. J Neurotrauma 15(8): 573-85. 1997.

25. Appendix 6 – Consultee & Patient Information Sheet

INFORMATION FOR CONSULTEE

Version, Date, Ethics Ref.No

International prospective observational Study on iNtrAcranial PreSsurE in intensive care (ICU): The SYNAPSE-ICU Study

Introduction

We feel your relative/friend is unable to decide for himself/herself whether to participate in this research. To help decide if he/she should join the study, we'd like to ask your opinion whether they would want to be involved. We'd ask you to consider what you know of their wishes and feelings, and to consider their interests. Please let us know of any advance decisions they may have made about participating in research. These should take precedence.

If you decide your relative/friend would have no objection to taking part we will ask you to read and sign the consultee declaration on the last page of this information leaflet. We'll then give you a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns or you think your relative/friend should be withdrawn.

If you decide that your friend/relative would not wish to take part it will not affect the standard of care they receive in any way.

If you are unsure about taking the role of consultee you may seek independent advice. We will understand if you do not want to take on this responsibility.

The following information is the same as would have been provided to your relative/friend.

1. What is the purpose of the study?

Intracranial pressure is often measured in the Intensive Care Unit when someone is admitted after an acute brain injury. High intracranial pressure is associated with worse outcome, and very high intracranial pressure is a life-threatening situation. However, whereas in certain part of the world this measurement is easily obtained, in others it is still not used routinely. We would like to collect as much information as possible to identify these differences worldwide, and create a map of how intracranial pressure is measured and what are the treatment used for high intracranial pressure around the world.

2. Why has my relative been chosen?

Your relative/friend was admitted to hospital for treatment of acute brain injury. However, he/she is now not capable of making an informed decision about whether he/she wishes to participate in the study or not. We would like you to consider whether your relative/friend would want to take part in this research.

3. What will happen to my relative?

If it is agreed, your relative/friend will not undergo any additional intervention/procedure. We will only collect data from the medical notes and enter them into an electronic database completely anonymised. The care your relative/friend will receive will not change at all from the standard practice of your hospital/Unit. We will contact him/her at 6 months via phone/mail/email to check on his/her progress after the acute brain injury and ask him/her some questions about his/her health. If your relative/friend has recover capacity to give informed consent at 6 months we will re-discuss participation in the study with him/her.

4. What are the possible benefits of taking part?

There are no direct benefits to your relative/friend taking part in this study, but information gained from this research might inform on the future healthcare of other patients.

5. What are the possible disadvantages and risks of taking part?

This study does not involve any additional investigation, intervention or procedure and does not carry any disadvantage or extra risk in participating.

6. What if there is a problem?

If you have a concern about any aspect of this study please contact [*name and contact details of local PI*] who will do their best to answer your questions.

7. What happens when the study is finished?

At the end of the study we will analyse the results and publish our findings in scientific journals and on our website. Your relative/friend will not be identifiable in any published results.

8. Confidentiality – Who will have access to the data?

All the information we collect during the research will be kept confidential and there are strict laws which safeguard your privacy at every stage.

Local study researchers will need access to your relative medical records/data to carry out this research.

We intend to store data outside your local healthcare/research, however your relative will not be identifiable in any database outside your local institution.

With your consent, we will inform the GP that your relative/friend are taking part.

To ensure that the study is being run correctly, we will ask your relative/friend consent for responsible representatives from the Sponsor [*Local PI*] to access your relative/friend medical records and data collected during the study, where it is relevant to your relative/friend taking part in this research. The Sponsor is responsible for overall management of the study and providing insurance and indemnity.

9. Who is organising the research and why?

This study has been organised/sponsored by University Milano Bicocca (Monza, Italy) and funded by the European Society of Intensive Care Medicine.

If you have any further questions about the study please contact xxxxx on: (xxx xxxx) or email: xxxxx@xxxxxx

If you would like to discuss this study with someone independent of the study please contact: xxxxx

If you wish to make a complaint about the study please contact XXX

Thank you for taking the time to read this information sheet.

26. Appendix 7 – Consultee Declaration Form (ENG)

(Form to be on headed paper)

CONSULTEE DECLARATION FORM

Centre Number:

Study Number:

Participant Identification Number for this study:

27. Appendix 8 – Template Informed Consent form (ENG)

(Form to be on headed paper)

PARTICIPANT INFORMATION SHEET AND CONSENT FORM RECOVERED CAPACITY

International prospective observational Study on iNtrAcranial PreSsurE in intensive care (ICU): The SYNAPSE-ICU Study

You are being invited to consider continuing to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask me if there is anything that is not clear or if you would like more information. Thank you for reading this.

Why am I already in this study?

During your recent admission to hospital you were unable to give consent for entry into a study, we therefore asked your nearest relative or welfare attorney or guardian who gave consent on your behalf to enter this study.

What is the purpose of the study?

Intracranial pressure is often measured in the Intensive Care Unit when someone is admitted after an acute brain injury. High intracranial pressure is associated with worse outcome, and very high intracranial pressure is a life-threatening situation. However, whereas in certain part of the world this measurement is easily obtained, in others it is still not used routinely. We would like to collect as much information as possible to identify these differences worldwide, and create a map of how intracranial pressure is measured and what are the treatment used for high intracranial pressure around the world.

Why were you chosen?

You were admitted to hospital for treatment of acute brain injury and your nearest relative or welfare attorney or guardian agreed that you could join the study. However, you are now capable of making an informed decision about whether you wish to continue in the study or not.

Do you have to continue to take part?

No. It is up to you to decide whether to take part in the research or not. If you decide to take part you will be free to change your mind at any time and without giving a reason and this will not in any way alter your care, now or at any stage in the future. If you decide to not continue you can allow all the information and samples collected so far to remain in the study, or if you prefer we can destroy all samples and information so that you will be completely removed from the study.

What will happen to you if you take part in the research?

If you agree to take part in the study, you will not undergo any additional intervention/procedure. We will only collect data from the medical notes and enter them into an electronic database completely anonymised. The care you will receive will not change at all from the standard practice of your hospital/Unit. We will contact you at 6 months from the acute brain injury via phone/mail/email to check on your progress and ask you some questions about your health.

What are the possible benefits of taking part?

There are no direct benefits to you taking part in this study, but information gained from this research might inform on the future healthcare of other patients.

What are the possible disadvantages and risks of taking part?

This study does not involve any additional investigation, intervention or procedure and does not carry any disadvantage or extra risk in participating.

What if there is a problem?

If you have a concern about any aspect of this study please contact [*name and contact details of local PI*] who will do their best to answer your questions.

What happens when the study is finished?

At the end of the study we will analyse the results and publish our findings in scientific journals and on our website. You will not be identifiable in any published results.

Will my taking part in the study be kept confidential?

All the information we collect during the research will be kept confidential and there are strict laws which safeguard your privacy at every stage.

Local study researchers will need access to your medical records/data to carry out this research.

We intend to store data outside your local healthcare/research, however you will not be identifiable in any database outside your local institution.

With your consent, we will inform your GP that you are taking part.

To ensure that the study is being run correctly, we will ask your consent for responsible representatives from the Sponsor [*Local PI*] to access your medical records and data collected during the study, where it is relevant to you taking part in this research. The Sponsor is responsible for overall management of the study and providing insurance and indemnity.

Who is organising the research and why?

This study has been organised/sponsored by University Milano Bicocca (Monza, Italy) and funded by the European Society of Intensive Care Medicine.

Who has reviewed the study?

The study proposal has been reviewed by the European Society of Intensive Care Medicine and the [Local Research Ethics Institution]. All research is looked at by an independent group of people, called a Research Ethics Committee. A favourable ethical opinion has been obtained from xxx REC. Management approval has also been obtained

If you have any further questions about the study please contact xxxxx on: (xxx xxxx) or email: xxxxx@xxxxxx

If you would like to discuss this study with someone independent of the study please contact: xxxxx

If you wish to make a complaint about the study please contact XXX

Thank you for taking the time to read this information sheet.

(Form to be on headed paper)

CONSENT FORM

Ethics Ref.no:

Centre Number:

Study Number:

Participant Identification Number for this trial:

Title of Project: **International prospective observational Study on iNtrAcranial PreSsurE in intensive care (ICU): The SYNAPSE-ICU Study**

Name of Researcher: *[name and contact details of local PI]*

Please initial box

- 1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
- 2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
- 3. (If appropriate) I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from [company name], from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
- 4. (If appropriate) I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.
- 5. (If appropriate) I agree to my General Practitioner being informed of my participation in the study. / I agree to my General Practitioner being involved in the study, including any necessary exchange of information about me between my GP and the research team.
- 6. (If appropriate) I understand that the information held and maintained by the Health and Social Care Information Centre (or amend as appropriate) and other central UK NHS bodies may be used to help contact me or provide information about my health status.
- 7. I agree to take part in the above study.

Name of Participant

Date

Signature

Name of Person
taking consent

Date

Signature

When completed: 1 (original) to be kept in care record, 1 for consultee; 1 for researcher site file