This protocol has regard for the HRA guidance and order of content; OR

FULL/LONG TITLE OF THE STUDY: Age Related Thresholds for management of severe head injury in Paediatrics- Extension of STARSHIP

SHORT STUDY TITLE / ACRONYM: ARTSHIP

PROTOCOL VERSION NUMBER AND DATE: Version 3.0, 24/06/2025

RESEARCH REFERENCE NUMBERS:

IRAS Number:	ARTSHIP: 356856, (STARSHIP: 321960)
SPONSORS Number:	A097390 (STARSHIP: A09469)
FUNDERS Number:	NA

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:

.....

Date:
...../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Date:

Signature:

Name:

LIST of CONTENTS

GENERAL INFORMATION	**Page No.**
HRA PROTOCOL COMPLIANCE DECLARATION	i
TITLE PAGE	i
RESEARCH REFERENCE NUMBERS	i
SIGNATURE PAGE	ii
LIST OF CONTENTS	iii
KEY STUDY CONTACTS	iv
STUDY SUMMARY	iv
FUNDING	v
ROLE OF SPONSOR AND FUNDER	v
ROLES & RESPONSIBILITIES OF STUDY STEERING GROUPS AND INDIVIDUALS	v
SECTION	
1. BACKGROUND	1
2. RATIONALE	1-2
3. THEORETICAL FRAMEWORK	2
4. RESEARCH QUESTION/AIM(S)	2
5. STUDY DESIGN/METHODS	2
6. STUDY SETTING	2-3
7. SAMPLE AND STATISTICAL ANALYSIS	3-4
8. ETHICAL AND REGULATORY COMPLIANCE	4-6
9. DISSEMINATION POLICY	6
10. REFERENCES	7

KEY STUDY CONTACTS

Insert full details of the key study contacts including the following

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Joint-sponsor(s)/co-sponsor(s)	NA
Funder(s)	NA
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Committees	NA

STUDY SUMMARY

Study Title	Age related thresholds for management of severe head injury in paediatrics: ARTSHIP
Internal ref. no. (or short title)	ARTSHIP
Study Design	Retrospective combine database study
Study Participants	Children less than or equal to 18 years of age requiring invasive monitoring in PICU for traumatic brain injury
Planned Size of Sample (if applicable)	NA, approximately 350-500 patients from combining datasets
Follow up duration (if applicable)	NA
Planned Study Period	01/10/2026- 31/09/2028
Research Question/Aim(s)	To combine existing datasets containing high-resolution physiological monitoring data combined with clinical and outcome details in children with traumatic brain injury (from other UK and international centres) to create a larger cohort 350-500 patients) of paediatric TBI (pTBI) patients. The larger dataset analysis will help stratify cerebral autoregulation guided treatment targets for neuroprotection across the paediatric age range and facilitate statistically meaningful

	analysis of age-stratified thresholds of treatment targets namely intracranial pressure (ICP), cerebral perfusion pressure (CPP) and cerebral autoregulation (PRx) using the same analytical used for STARSHIP.

FUNDING AND SUPPORT IN KIND: NA

ROLE OF STUDY SPONSOR AND FUNDER

Aim: To clarify the potential influence of sponsor and funders over the study

The sponsor has no direct influence in study design, conduct, data analysis and interpretation including writing manuscripts and dissemination of results. There is no funding/funder for the project.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS- NA

KEY WORDS: CPP, ICP, PRx, CA, Paediatric, TBI, head injury

STUDY PROTOCOL: Age Related Thresholds for management of severe head injury in Paediatrics- Extension of STARSHIP (ARTSHIP)

1. Background

Neuro-morbidity associated with TBI in children is high and there is limited available evidence for strategies to improve outcomes[1]. The last international guideline for management of severe TBI in children were mainly based on level III evidence due to lack of robust evidence for age related thresholds for treatment targets in paediatric intensive care (PICU) like intracranial pressure (ICP) and cerebral perfusion pressure (CPP), or availability of methods to individualise these targets, like indices of cerebral autoregulation (CA)[2]. As the paediatric age range encompasses a developmental trajectory, combined with the disease heterogeneity, single treatment thresholds are insufficient for the best outcomes in paediatric TBI (pTBI). Given the ethical challenges and difficulties with doing research in children and poor yield from randomized controlled trials, there is increasing recognition of using big data to answer research questions.

We have recently completed the multicentre prospective research database study, STARSHIP including 135 pTBI patients with promising results confirming PRx association with outcome irrespective of the initial disease severity, ICP and CPP, and centre specific differences in management[3]. We have also identified dynamic temporal trends of PRx and its thresholds for outcome. In this process, we have also created a rich research database with time-synchronized physiological information with clinical and outcome data which has been used to further explore the thresholds for ICP and CPP related to outcome. However, the small number of patients in each age category does not allow identification of age-appropriate thresholds. STARSHIP has ethics approval as a research database which allows for the database to be combined with other databases. There are similar datasets that exists in individual centers, for eg, Addenbrookes Hospital prior to STARSHIP, Birmingham Children's Hospital in the UK, Phoenix Children's Hospital in the USA, Uppsala University in Sweden, to name a few. Given the small numbers of pTBI, all these centers have come together to collaborate to make a meaningful impact by combining datasets.

Through this project, we propose to combine similar existing datasets from other UK and international centres to create a larger cohort (350- 500 patients) of pTBI patients. This will facilitate statistically meaningful analysis of age-stratified thresholds, namely ICP, CPP and PRx using the same analytical methods we have used for STARSHIP[3,4]. The larger dataset analysis may help stratify CA guided treatment targets for neuroprotection across the paediatric age range.

2. Rationale & Theoretical Framework

We will use the combined dataset to identify age-appropriate treatment thresholds for neuroprotection, i.e., ICP and CPP in severe pTBI for improved outcomes as well test if the PRx thresholds are

different in different age ranges. The results of this study would be crucial to fill some of the gaps in current evidence base for managing children with severe TBI. This will help with planning future prospective interventional studies to evaluate if the age-appropriate and CA guided treatment thresholds can improve outcomes in children with TBI.

The study will help stratification of age-based thresholds for treatment targets used in managing severe pTBI with the hypothesis that there would be different thresholds for ICP and CPP depending on the patients age and autoregulatory status. The results should inform the international evidence-based guidelines as well as future research by creating foundation for phase II/III studies to test the hypothesis in prospective clinical studies.

3. Research Question/Aims and Objectives:

To identify age-stratified thresholds of treatment targets for neuroprotection, namely intracranial pressure (ICP), cerebral perfusion pressure (CPP) and cerebral autoregulation (PRx) in children with traumatic brain injury.

4. Study Design/ Methods:

We will use the combined dataset to identify age-appropriate treatment thresholds for neuroprotection, i.e., ICP and CPP in severe pTBI for improved outcomes as well test if the PRx thresholds are different in different age ranges. The results of this study would be crucial to fill some of the gaps in current evidence base for managing children with severe TBI. This will help with planning future prospective interventional studies to evaluate if the age-appropriate and CA guided treatment thresholds can improve outcomes in children with TBI. The study will help stratification of age-based thresholds for treatment targets used in managing severe pTBI with the hypothesis that there would be different thresholds for ICP and CPP depending on the patients age and autoregulatory status. The results should inform the international evidence-based guidelines as well as future research by creating foundation for phase II/III studies to test the hypothesis in prospective clinical studies.

Dataset	**Number of pTBI patients**
STARSHIP, UK	135
Cambridge pTBI cohort, UK	35
Birmingham pTBI cohort, UK	20
Uppsala University pTBI cohort, Sweden	90
Phoenix Children's Hospital, USA	200
Sophia Children's Hospital, Erasmus	80
UZ Leuven, Belgium	15

Table 1: Existing datasets for analyses

5. **Study setting:** Inclusion criteria- Datasets containing at least 15 pTBI patients upto 18 years of age with advanced neuromonitoring data, consisting of high-resolution (≥100Hz) waveform data with minimum 6 hours of recording along with clinical and demographic details defining severity of pTBI and 6 months follow-up post-ictus will be included.
   i) Full-resolution physiological monitored data in PICU (mainly ICP and arterial blood pressure, ABP; if available $ETCO_2$, ECG, Temperature)
   ii) Clinical details- demographic data (age, sex, weight, injury details including type, severity and mechanism, post resuscitation Glasgow coma scale (GCS), pre-hospital cardio-pulmonary resuscitation (CPR), pre-hospital hypoxia, hypotension, hyperthermia, admission pupillary size and response], disease and injury severity scores, treatment for traumatic brain injury (medical & surgical), head computerized tomography (CT) scan at admission). If available, we will also collect ventilatory parameters (oxygenation and ventilation parameters), laboratory analyses (Haemoglobin, sodium, glucose, lactate etc.).
   iii) Outcome follow-up at least upto 6 months with GOS extended for Pediatrics (GOSEP) or GOS or PCPC and if available upto 12 months outcome.
6. **Sample & Statistical Methods:** After completing the data sharing agreements and processes required to combine the datasets in the 1st quarter, we will complete harmonization of physiological measurements as well as clinical and follow-up data from the different datasets, including time synchronization of the clinical annotations with the physiological recordings. We will collect the pre-processed data from each centre which would have undergone the artefact cleaning and preliminary analysis; depending on the data sharing agreement, will either get the hdf files or the processed data from the ICM+ with harmonized configurations. For the unprocessed data, after pre-processing including harmonization and careful, standardised, curation, time-averaged values of ICP, CPP, PRx and CPPopt will be calculated using waveform time integration over 60-sec intervals. This will be followed by general data audit and evaluation of per-centre differences. We will also take account of the missingness of the data/variables in the datasets and use valid imputation methods where applicable. This will lead to creation of a single, homogeneous, data set for further processing. Finally, a set of statistical models will be applied to the data in age-stratified groups. Data will be hosted in the Brain Physics Lab, University of Cambridge server and the analysis will be performed under supervision of the lab which has 3 decades of experience in data curation, handling and analysis. The calculated ICP and CPP values would be used to identify the thresholds of each against the 6- and 12-months outcome in 6 different age categories: ≤1, 1-3, 3-5, 5-8, 8-11, 11-16 years, respectively and receiver operating curves created for individual age categories. Previously validated methods will be used to calculate ICP, CPP and PRx dose response above or below these identified thresholds to further understand the strength of their

association with outcome. There will be further exploratory analysis of ICP/CPP targets in relation to the state of CA.

Statistical methods: Appropriate statistical methods will be employed to account for initial disease severity (propensity score calculation and sliding dichotomy, propensity score matching), and centre related differences (mixed effects model) which we have used for analysing STARSHIP results. Bias reducing techniques, like 5-fold cross-validation, will be applied, where appropriate, for age dependent thresholds derivations. Continuous variables will be assessed for normality and expressed as mean (SD) or median (interquartile range), depending on the underlying distribution of the data. Categorical variables will be reported as counts and proportions. Differences in physiological values between survivors and non-survivors will be interrogated with the Mann-Whitney U-test for non-normally distributed continuous variables, Student t test for normally distributed continuous variables and Fisher exact test for categorical variables. All tests will be two-tailed and unadjusted for multiple comparisons. Spearman rank correlation coefficient (ρ) will be used to see correlations between variables. Identification of critical threshold values of PRx for predicting unfavorable outcome will be performed using iterative chi-square tests, as per the method used in STARSHIP analysis. To account for any possible confounding effect of the differing periods of monitoring and day post admission on which monitoring starts on outcome associations, ordinal logistic regression analysis will be performed. The independent effect of each continuously monitored variable on the outcome will be assessed by including the length of monitoring and monitoring commencement day post admission as covariates in the regression models. For those predictors that are concentrated around 0 (e.g., PRx and percentages of monitoring time expressed as fractions), the raw values will be multiplied by 10 to enable a meaningful interpretation of odds ratios in the regression analyses. The effect of time on PRx will be assessed using repeated-measures analysis of variance with each patient treated as a random effect.

Risks/Benefits: There are no risks as the project only involves retrospective analysis of previously collected anonymised datasets from the routinely monitored and collected data from the bedside monitors and clinical notes. The datasets will not include any patient identifiable information including even year of birth, we will only collect the patient's age at the time of ictus. The project does not accrue any direct benefit to the participants but will provide the scientific community with much needed information and resource to answer important questions which may help in improving management and outcome of children with severe TBI in the future.

7. Ethical and Regulatory Consideration

The STARSHIP database has the ethics approval to incorporate other datasets.

Confidentiality: As highlighted above, the project involves analysis of combined datasets consisting of anonymised, de-identified information from previously approved (prospective research studies with direct patient consents or datasets collected as a part of institutional policy/approvals with implied consent). There is no patient identifiable information collected for the purposes of this project. We will protect patient-subject identifiers from improper use and disclosure is consistent with our plans to protect the overall data of the study. Each subject within the respective dataset would already have a unique, de-identified study ID and this study ID will be utilized for importing data to the study database. Details of the GDPR compliance are attached in Annex 1.

Consent: There is no consent required for the project as we will be using databases which have ethics/institutional approvals with pre-consented data. The data sharing agreements will undergo individual centre/data holder's rigorous scrutiny before the final databases are shared and combined.

Security Arrangements**:** Appointed data manager will be responsible for monitoring data transfer to Cambridge, for data verification, validation and repackaging, and storing it in the Archive location on the same server. The key file, containing data source identifiers will be kept entirely separate, by the project main applicant. Full ethical and legal practice will be followed, and database will be managed securely under the supervision of data custodian. The data will be stored in a secure server located on a private network behind a tight firewall, in the Brain Physics Lab, Division of Neurosurgery, Department of Clinical Neurosciences, CUH. We will use the already established system in use for STARSHIP project. All the clinical, demographic and telephone follow-up interview data elements collected will be stored under the allocated anonymised study ID. The paper-based copies will be stored in a secure room within each centre behind locked doors and locked cupboards with limited access to the study personnel. This anonymised data will be shared with CUH and stored on a secure computer behind the firewall with the same mechanisms in place as described above.

Management of Database: The data will be stored in a secure server located on a private network behind a tight firewall, in the Brain Physics Lab, Division of Neurosurgery, Department of Clinical Neurosciences (details described above). Appointed data manager will be responsible for monitoring data transfer to Cambridge, for data verification, validation and repackaging, and storing it in the Archive location on the same server. Full ethical and legal practice will be followed, and database will be managed securely under the supervision of data custodian.

The shared data will only be used for pre-agreed purposes and approved analyses in agreement with all the individual data-controllers. All the shared information will be kept confidential and secure. It will not be shared in any form or format with anyone outside the study team and will be deleted, including all copies of the original data, following completion of the project. The collaboration will be acknowledged in all the research outputs from the combined analysis.

Access to Database**:** The database will only be accessible to the study personnel within CUH. Till the end of the project, the combined dataset will be available to each contributing centre for analysis and projects which will be discussed in the study steering committee and the information governance department at CUH).

Declaration of Helsinki and ICH Good Clinical Practice: The project is to be carried out in conformation with the spirit and the letter of the declaration of Helsinki, and in accord with the ICH Good Clinical Practice Guidelines.

Agreement with Host Organisation about Electronic storage**:** CUH and the Academic Department of Clinical Neurosciences have experience in establishing and managing electronic data and database. There is full agreement for electronic storage in a secure manner as detailed above. The team has set-up data collection for a similar adult TBI international multi-centre study (CENTER TBI).

8. Dissemination and Possible Linkage to other databases/registries:

The results will be disseminated with presentations and publications at national/international conferences and peer-reviewed journals. The data extracts from the different studies will be uploaded to TBI-REPORTER platform to facilitate integration of combined second-stage analysis of datasets. In future, based upon the analysis and the data collected in this project, we will endeavour to identify further funding and national and international collaboration to help scientific understanding and improve patient outcomes.

9. Information Governance

The application and the database management and monitoring have full support from the patient safety department at CUH and the protocol has been approved by them. The entire project will be conducted under close scrutiny of data custodian and the patient safety department.

10. End of the study

After acquisition of the datasets, the datasets will be merged after cleaning and harmonization and curated for analysis. Once the combined dataset is created for ARTSHIP, the data analyses will take upto one year.

References:

1. Dewan MC MN, Wellons III C, Bonfield CM. Epidemiology of Global Pediatric Traumatic Brain Injury: Qualitative Review. *World Neurosurg* 2016; **91**: 497-509.

2. Kochanek PM, Tasker RC, Carney N, et al. Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, Third Edition: Update of the Brain Trauma Foundation Guidelines. *Pediatr Crit Care Med* 2019; **20**(3S Suppl 1): S1-S82.

3. Agrawal S, Smith C, Bogli SY, et al. Status of cerebrovascular autoregulation relates to outcome in severe paediatric head injury: STARSHIP, a prospective multicentre validation study. *EClinicalMedicine* 2025; **81**: 103077.

4. Sorrentino E DJ, Ksprowicz M, Budohoski KP, Haubrich C, Smielewski P, Outtrim JG, Manktelow A, Hutchinson PJ, Pickard JD, Menon DK, Czosnyka M. Critical thresholds for cerebrovascular reactivity after traumatic brain injury. *Neurocrit Care* 2012; **16**: 258-66.

Annex 1: GDPR compliance

The study will be conducted in compliance with the requirements of the GDPR and abide by the relevant country's laws implementing the GDPR (including the Belgian Law of July 30th 2018) on the protection of natural persons with regard to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix). In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR.

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

The participating site, the Investigator and Sponsor shall have and maintain in full force and effect during the term of this study, and for a reasonable period following termination of the study, adequate insurance coverage for: (a) medical professional and/or medical malpractice liability, and (b) general liability.

(i) ***For Belgian participating sites***

Art 29 of the Belgian Law relating to experiments on human persons dated May 7th, 2004 applies.

Prior to the start of the study, the Sponsor shall enter into an insurance contract in order to adequately cover study participants from Belgian sites in accordance with art. 29 of the said law.

(ii) ***For non-Belgian participating sites (if applicable)***

The participating site shall have and maintain in full force and effect during the term of this study (and for a reasonable period following termination of the study, adequate insurance coverage for other possible damages resulting from the study at the participating site, as required by local law. Each such insurance coverage shall be in amounts appropriate to the conduct of the services of the participating site under this study.

The participating site and Sponsor shall be solely responsible for any deductible or self-insured retention under any such policies.

As specified in GCP, the Sponsor and Investigator/participating site(s) will maintain a record of the location(s) of all respective essential study documents (including but not limited to source documents, completed and final eCRF and ISF/TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the eCRF data reported to the sponsor during the study.

The Investigator/participating site should have control of all essential study documents and records generated by the Investigator/participating site before, during and following termination of the study.

Study-specific documentation (such as but not limited to the study protocol, any modifications thereto, the final Clinical Study Report (CSR) and the study database), as well as source data and site-specific study documents (such as but not limited to the original signed ICFs) will be archived by the participating site(s) according to local practice, and for at least 25 years following termination of the study. Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained if required, and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of essential study documents prior to, during or upon completion of the required archival period, will require written authorisation from the Sponsor.