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

FULL/LONG TITLE OF THE STUDY: Prognostic model for predicting outcomes after moderate to severe Paediatric Traumatic Brain Injury

SHORT STUDY TITLE / ACRONYM: **Pro**gnostic **M**odel for **P**aediatric **T**BI

PROTOCOL VERSION NUMBER AND DATE: Version 1.0, 21/03/2025

RESEARCH REFERENCE NUMBERS:

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LIST of CONTENTS

KEY STUDY CONTACTS

Insert full details of the key study contacts including the following

Chief Investigator	Dr Shruti Agrawal Consultant in Paediatric Intensive Care PICU, Level 3, Box 7 Cambridge University Hospitals, Hills Road Cambridge CB2 0QQ Ph: +44(0) 1223 348 066 Email: shruti.agrawal1@nhs.net, sa882@cam.ac.uk
Study Co-ordinator	NA
Sponsor	Dr Stephen Kelleher R&D Manager, Research and Development Department Cambridge University Hospitals Hills Road, Cambridge CB2 0QQ Ph: +44(0)1223 349 302 Email: cuh.research@nhs.net
Joint-sponsor(s)/co-sponsor(s)	NA
Funder(s)	NA
Key Protocol Contributors	Dr Shruti Agrawal & Professor Ewout Steyerberg
Committees	NA

STUDY SUMMARY

Study Title	Prognostic model for predicting outcomes after moderate to severe Paediatric Traumatic Brain Injury
Internal ref. no. (or short title)	PROMPT
Study Design	Retrospective combine database study
Study Participants	Children less than or equal to 18 years of age with moderated to severe traumatic brain injury
Planned Size of Sample (if applicable)	NA
Follow up duration (if applicable)	NA
Planned Study Period	01/06/2025- 30/06/2026
Research Question/Aim(s)	To create and validate a paediatric specific prognostic model for outcomes following moderate to severe TBI for use in both resource-limited and resource-rich environments. Our hypothesis is that the performance of the current adult TBI prognostic models in predicting outcomes following pTBI can be improved by introducing age-appropriate modifications to the existing models.

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: Prognostic model, Paediatric, TBI, head injury

STUDY PROTOCOL: Prognostic model for predicting outcomes after moderate to severe Paediatric Traumatic Brain Injury (PROMPT)

1. Background

The healthcare, societal and economic impact from paediatric traumatic brain injury (pTBI) is one of the greatest unmet needs with estimates suggesting upto 2/3rd of survivors developing life-long neurological deficits[1]. Due to ethical and logistical challenges related to paediatric research, there is limited age-appropriate evidence for children which perpetuates the funding gaps further confounding the lack of evidence[2]. However, extrapolation of adult TBI research evidence to children is inaccurate and inappropriate given the differences in mechanisms and patterns of injury, pathophysiological responses and neurological recovery from it, in the context of developmental trajectory[3,4]; hence, robust evidence is required to improve outcomes from pTBI as well as facilitate research collaborations.

The prognostic models used for adult TBI research (IMPACT, CRASH)[5,6] and imaging criteria (Marshall and Rotterdam scores)[7,8], have been derived and validated from analysis of large international datasets which have undergone further validation in multiple prospective studies[9]; the wide use of these prognostic models across neurotrauma research highlights the relative simplicity and the variables used for prediction making them applicable to both low and high resource set-ups. This has facilitated international collaborative research in adult TBI; however, no such models exist for pTBI with most pTBI research continuing to use adult prognostic models[10,11]. Though the variables used for these models show association with outcome in pTBI as well, there are multiple issues with this approach with the key difficulty being the age variable. In the adult models, the younger age is expected to be associated with better outcome; for CRASH, the model is likely weighed heavily towards non-age variables as the younger patients are expected to do better with patients between 18-40 lumped as <40 years and for IMPACT, slightly better which accounts for 14 years and above. However, the balance between neuroplasticity and neurodevelopmental trajectory in paediatric age group is difficult to predict with evidence suggesting worse neuro-developmental outcomes after TBI in younger children. Hence the adult models can either over- or under-predict neurological outcomes in pTBI and have never been validated in pTBI datasets.

2. Rationale & Theoretical Framework

A validated predictive model for pTBI would be the first step towards collaborative research and identifying age-appropriate benchmarks for pTBI research studies as well as to complement an individual child's clinical assessment, treatment decisions, informing families and resource allocation. Given that the amount of data required to create pTBI predictive model is difficult to collect and the reasonable validity of adult prognostic models in pTBI, albeit in small single-centre studies, we propose to create paediatric modification to the adult models and identify a robust pTBI predictive model for improved classification of injury severity to predict disease trajectory and outcome as well as stratification of patients for interventional research and benchmarking in pTBI to help with appropriate resource allocation for neuro-interventions towards improved outcomes.

3. Research Question/Aims and Objectives:

To create and validate a paediatric specific prognostic model for outcomes following moderate to severe TBI for use in both resource-limited and resource-rich environments. Our hypothesis is that the performance of the current adult TBI prognostic models in predicting outcomes following pTBI can be improved by introducing age-appropriate modifications to the existing models.

4. Study Design/ Methods:

We will use combined retrospective pTBI datasets (moderate to severe TBI in children ≤ 18 years); Table 1 shows the approximate number and outcome distribution of the datasets currently ready for this collaboration with ongoing discussions for combining more datasets.

Dataset	Number of moderate to severe pTBI	Outcome: Non-survivors
STARSHIP-extended	724	89
ADAPT	1000	129
CENTER-TBI	177	7
Total	2001	225

Table 1: Existing datasets for analyses

5. **Study setting:** We will collect the following variables for children affected with moderate to severe TBI from the pre-existing datasets

Variables	Essential	Desirable
Admission	• Age • Sex • GCS • Motor Score • Pupils • AIS and ISS • Mechanism of Injury	• Pre-hospital hypoxia and/or hypotension • Pre-hospital cardiac arrest • Major extra cranial injuries • Blood Glucose • Full blood count, coagulation profile • Electrolytes • Lactate • CT variables*
Outcome	6 months GOS or PCPC	• 2 weeks GOS or mortality • 6 mo GOS Extended Pediatrics (GOSEP)

**CT variables: Blood (ICH, SDH, EDH, SAH, IVH, contusions), pressure (Cisterns, midline shift)*

Table 2: Variables to be collected

6. Sample & Statistical Methods:

There is no defined sample size for the study. We will aim to collect datasets which contain the variables mentioned in table 2 from children with moderate to severe TBI upto the age of 18 years. There are no exclusion criteria for the study. All the datasets will either be from a prospective study (ethics approved with valid consent) and/or datasets created for audit/institutional purposes with appropriate approvals from local/national research committees and contain anonymised non-identifiable information.

The analysis will include specific and important considerations for pTBI listed as below:

- Representation across the age range (pTBI has two peaks, under one year and then adolescent age group).
- Lower mortality as compared to adult TBI, important that model predicts poor neurological outcome.
- Non-accidental injury as unlikely to be a single injury, but equally an important group in pTBI who are traditionally omitted from research and consider including mechanism as a variable for analysis if adequate data.
- Imputing for missing data.

Model development and performance:

- Assess performance of the available models, namely, CRASH (basic and CT), IMPACT (core, extended and lab) and Marshall, Rotterdam and Helsinki CT criteria. Performance includes assessments of discrimination and calibration.
- Create a stratified pTBI prediction model (for use in low vs high resource settings), with basic data (where limited variables are available) and extended (which may become better with additional variables where available) using logistic regression, internal and external validation, considering predictors from existing models and recent literature as a basis
- Compare the performance of different models in predicting outcomes from pTBI, dropping one cohort at a time (internal – external cross-validation).

Statistical Analysis:

Classic regression analysis approaches will be followed for prediction model development; including modern estimation with L1 and L2 penalties in LASSO and Ridge regression models.

- We will also explore application of available Machine learning (ML) tools: neural networks/support vector machine, SVM and random forest as examples of tools which have been used.
- For internal – external cross-validation, sample size in validation cohorts should preferably have at least 100 events; smaller sample sizes may be used with caution, and attempts will be made to combine smaller cohorts with similar cohorts where possible.
- Standard performance measures will be used for discrimination (area under the ROC curve) and calibration (baseline risk miscalibration with a model intercept; overall miscalibration with a slope parameter)[12,13].

7. Ethical and Regulatory Consideration

Consent and Confidentiality: The data collection part of this study is limited to using variables required for the model development from anonymized existing datasets. There is no additional data collection for the study purposes beyond what is already available in the ethics approved/consented datasets either as a part of a multicentre research study or approved institutional data collection. Only the de-identified dataset consisting of the study variables will be shared for the study purposes.

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.

IT security and access to database**:** The data will be stored in a secure server located on a private network behind a tight firewall. It will only be accessible to the study personnel as outlined above.

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. References:

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