

BMJ Open PRECISION-TBI: a study protocol for a vanguard prospective cohort study to enhance understanding and management of moderate to severe traumatic brain injury in Australia

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ABSTRACT

Introduction Traumatic brain injury (TBI) is a heterogeneous condition in terms of pathophysiology and clinical course. Outcomes from moderate to severe TBI (msTBI) remain poor despite concerted research efforts. The heterogeneity of clinical management represents a barrier to progress in this area. PRECISION-TBI is a prospective, observational, cohort study that will establish a clinical research network across major neurotrauma centres in Australia. This network will enable the ongoing collection of injury and clinical management data from patients with msTBI, to quantify variations in processes of care between sites. It will also pilot high-frequency data collection and analysis techniques, novel clinical interventions, and comparative effectiveness methodology.

Methods and analysis PRECISION-TBI will initially enrol 300 patients with msTBI with Glasgow Coma Scale (GCS) <13 requiring intensive care unit (ICU) admission for invasive neuromonitoring from 10 Australian neurotrauma centres. Demographic data and process of care data (eg, prehospital, emergency and surgical intervention variables) will be collected. Clinical data will include prehospital and emergency department vital signs, and ICU physiological variables in the form of high frequency neuromonitoring data. ICU treatment data will also be collected for specific aspects of msTBI care. Six-month extended Glasgow Outcome Scores (GOSE) will be collected as the key outcome. Statistical analysis will focus on measures of between and within-site variation. Reports documenting performance on selected key quality indicators will be provided to participating sites.

Ethics and dissemination Ethics approval has been obtained from The Alfred Human Research Ethics Committee (Alfred Health, Melbourne, Australia). All eligible participants will be included in the study under a waiver of consent (hospital data collection) and opt-out (6 months follow-up). Brochures explaining the rationale of the study will be provided to all participants and/or an appropriate

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Establishes a data collection network of 10 neurotrauma centres throughout Australia capturing patient-level data on demographics, clinical management and outcomes.
- ⇒ Collects common data elements for multiple embedded prospective moderate to severe traumatic brain injury (msTBI) trials.
- ⇒ The study will feedback performance data to participating hospitals to drive improvements in msTBI management.
- ⇒ This is the first stage in a longitudinal data collection project. The sample size of 300 patients will not be sufficient to perform definitive comparative effectiveness research.

medical treatment decision-maker, who can act on the patient's behalf if they lack capacity. Study findings will be disseminated by peer-review publications.

Trial registration number NCT05855252.

INTRODUCTION

Moderate to severe traumatic brain injury (msTBI) is a leading cause of death and disability and is a significant global public health problem.¹ In Australia, approximately 20 000 patients a year are admitted to hospitals with msTBI.² Unfortunately, short-term in-hospital mortality for severe TBI remains static at around 25%–30%, and many surviving patients suffer permanent neurological

disability³ despite management in well-resourced, integrated healthcare systems such as Australia. The resources required to care for patients with msTBI in the acute hospital setting, and in the community over the course of a lifetime of disability are enormous, and the economic (up to \$A2 billion annually in Australia²) and social costs of brain injury are unacceptably high.

A significant research effort has been applied to the management of critically ill patients with msTBI, focused primarily on stand-alone interventions (eg, therapeutic hypothermia⁴, decompressive craniectomy⁵ and erythropoietin administration⁶). These studies have answered important clinical questions, but unfortunately, have not provided novel efficacious treatments. One key reason for this lack of significant research progress is the inherent complexity and heterogeneity of msTBI, both as a pathological entity and a clinical syndrome. This dual heterogeneity introduces multiple unrecorded variables, and multiple non-linear interactions between these variables, such that attempts to identify effective individual treatments or bundles of care are often significantly confounded.⁷ Research aiming to identify a ‘magic bullet’ for msTBI may, therefore, be unrealistic and unlikely to succeed.⁷

The common feature of all msTBI is aetiological—damage to cerebral tissue resulting from application of force to those tissues. While the nature and magnitude of force impacting the brain has significant influence on eventual outcome, it is not the sole determinant. Rather, it is the starting point of a process of pathophysiological evolution involving a complex of multiple interdependent responses to injury that may reinforce or amplify each other causing further neurological damage.⁸ Running parallel to these evolving pathophysiological processes is the process of care for patients with msTBI. This involves a series of clinical phases, from prehospital care, emergency department management, surgical intervention, intensive care management and rehabilitation in the hospital ward and eventually the community. Throughout this process, there is the possibility to positively influence the pathophysiological evolution of damage to cerebral tissue with optimal clinical management.⁹

The significant influence of variation in ‘standard’ care of msTBI on outcome was starkly revealed by a study analysing outcomes for 9578 patients with msTBI. After adjustment for patient characteristics, there was a 3.3-fold difference in the odds of unfavourable outcome between centres.¹⁰ The subsequent recognition of the importance of variations in clinical management led to a reassessment of approaches to msTBI research and the completion of two large scale prospective observational cohort studies in the European (CENTER-TBI)¹¹ and North American (TRACK-TBI)¹² context. These studies provided further confirmation of the wide variation in msTBI management practices and demonstrated the influence these variations had on patient-centred outcomes.^{13 14} Despite accumulating evidence that variability in acute care significantly influences both clinical outcomes and healthcare costs in

msTBI, this has not been scrutinised at a national level in Australia.

PRECISION-TBI is a prospective observational cohort study of msTBI management in Australia. In line with recommendations for comparative effectiveness research from the Institute of Medicine,¹⁵ the study will use broad inclusion criteria (provided in full below) encompassing the full range of msTBI, collection of data on the use of current best practice, general systemic organisational factors and pathology specific clinical interventions. Data will also be collected for a duration sufficient to assess outcomes (6 months postinjury). In addition, the study design is in line with recommendations from the International initiative for Traumatic Brain Injury Research¹⁶ as it will use an observational design that collects data continuously, but also provides a framework for embedded clinical trials. An additional aim of the study is to develop a network of academic and clinical researchers in msTBI linking 10 of the major neurotrauma centres in Australia. This study will provide the infrastructure necessary to establish and maintain a robust data collection system that supports near real time neuromonitoring data collection. This network will, in turn, support ongoing data collection, research and innovation in the clinical management of msTBI.

Opportunities and future research plans

The first major research projects attempting to unify the collection of pathophysiological and clinical management data of msTBI are the CENTER-TBI and TRACK-TBI studies. These projects have collected large data sets and continue to provide key insights into how TBI can be more effectively managed. These studies have the advantage of large data sets. However, they suffer from significant drawbacks in terms of confounding factors external to clinical management data, introduced by the heterogeneity of healthcare system structure and differing models of care.¹⁷ In addition, this heterogeneity is a significant barrier to the implementation of changes to optimise management and reduce the impact of these external factors. PRECISION-TBI represents a unique opportunity. It will be the first large scale study of clinical care practices, intensive care unit (ICU) management and high frequency data collection performed in multiple centres within a unified healthcare system. This will facilitate an appraisal of variations in clinical management without the confounding factors generated by variations in models of care. PRECISION-TBI also provides an opportunity to survey experts in msTBI clinical management and research to establish benchmarks of high-quality care, record performance of sites against those benchmarks, feedback results to sites and demonstrate progress towards improvements in clinical management and patient outcomes. This process is in line with the concepts of a ‘learning healthcare system’ and continual improvement. Moreover, in future iterations of the study, it will hopefully be possible to collect additional more

granular information on neurorehabilitation, as variations in subacute and chronic care may also significantly impact longer-term outcomes.

OBJECTIVES

The primary objective of this study is to develop an ongoing, nationally representative data collection framework that will prospectively capture granular patient-level data relevant to the acute care of patients with msTBI admitted to the ICU requiring invasive neuromonitoring. These data will be used to:

1. Identify, record, track and benchmark clinical and logistical factors associated with outcomes in critically ill patients with msTBI in neurotrauma centres across Australia.
2. Pilot comparative effectiveness research initiatives using variations in clinical practice between sites as surrogate interventions with a particular focus on the clinical management of raised intracranial pressure (ICP).
3. Provide participating sites with specific feedback about patient characteristics and performance against a series of mutually agreed benchmarks.
4. Collect a set of common data elements for a series of small prospective clinical trials embedded within the larger PRECISION-TBI framework.

HYPOTHESIS

In adult patients admitted to ICU for the acute management of msTBI, variations in clinical care, such as the management of raised ICP and cerebral perfusion pressure (CPP), will be associated with significant differences in 6-month functional neurological outcomes.

STUDY OUTCOME MEASURES

The primary outcome is an unfavourable extended Glasgow Outcome Score (GOSE)¹⁸ at 6 months post-injury (defined as a score of 4 or less on the 8-point scale). Secondary outcomes will include mortality, ICU and hospital length of stay, and unit performance relative to key performance benchmarks, as identified by a modified Delphi process surveying experts actively involved in msTBI clinical management and research.

METHODS

The development of the protocol was conducted in accordance with The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP) principles, and the National Health and Medical Research Council (NHMRC)¹⁹ and Strengthening Reporting of Observational Studies in Epidemiology²⁰ guidelines. These principles will also guide the reporting of results.

Patient and public involvement

PRECISION-TBI has been designed in coordination with consumer representatives and a range of clinicians (including senior and junior medical staff and senior and junior nursing staff from neurosurgical, intensive care, emergency and rehabilitation medicine) with direct experience of msTBI either through lived experience or direct experience of caring for patients with msTBI. These groups are from geographically diverse areas of Australia and have had the opportunity to contribute to the development of the study protocol and design.

Study design

PRECISION-TBI is designed as an ongoing multicentre, prospective, observational, cohort study with capacity for smaller scale prospective trials embedded within the data collection framework. The first phase will enrol 300 participants over 3 years to test the data collection systems, reporting infrastructure and ability to embed novel interventions. Subsequent phases of the project will expand data collection to additional sites with ongoing recruitment of patients with msTBI and increased data linkage. Figure 1 illustrates the overall design of the study, including the pathway of participants through the study, dataflow and expected outputs from collected data. The study commenced recruiting patients in August 2022, with anticipated completion of enrolment and follow-up of the initial 300 patients in July 2025.

Study setting

This study will be coordinated by the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Monash University (Melbourne, Victoria). Participant recruitment and data collection will occur at ten Australian acute care hospitals verified as level 1 trauma centres (or equivalent): The Alfred and Royal Melbourne Hospital (Melbourne, Victoria), Royal Adelaide Hospital and Flinders Medical Centre (Adelaide, South Australia), Westmead Hospital, Royal North Shore Hospital and St George Hospital (Sydney, New South Wales), John Hunter Hospital (Newcastle, New South Wales) Royal Brisbane and Women's Hospital (Brisbane, Queensland) and Royal Perth Hospital (Perth, Western Australia). Data collection (including follow-up data) will conclude 6 months after the last participant is enrolled. Information about the study will be regularly updated on the PRECISION-TBI website: <https://www.monash.edu/medicine/sphpm/anzirc/research/precision-tbi-trial>.

Recruitment

Participants are eligible for enrolment into the study if they are adult patients (age ≥18 years), with a clinical diagnosis of msTBI (GCS<13 following head injury and in the absence of confounders) and admitted to the ICU with a requirement for invasive neuromonitoring as per the treating clinical team. Multitrauma patients and those with pre-existing neurological disease are eligible for inclusion. Enrolment must occur within 48 hours of

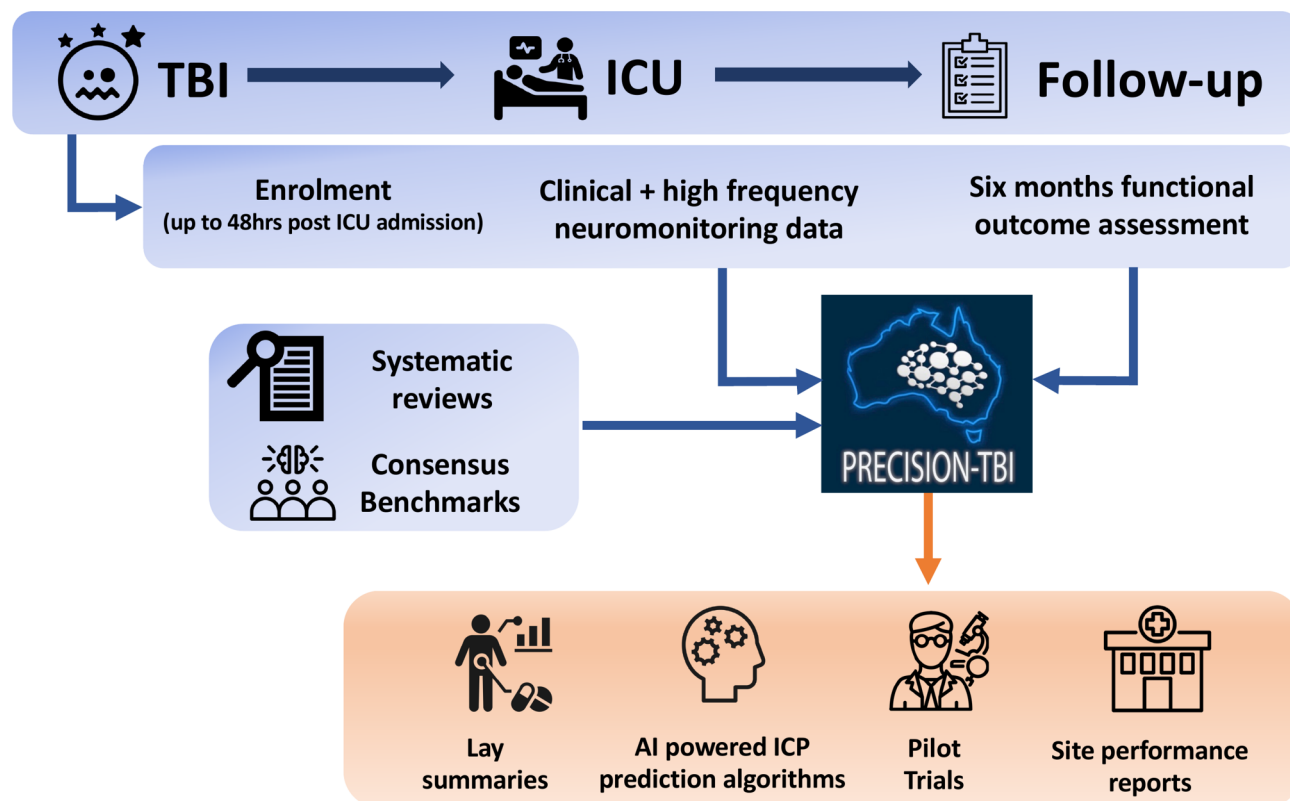


Figure 1 Schematic illustration of the study design and dataflow. ICP, intracranial pressure; ICU, intensive care unit; TBI, traumatic brain injury.

ICU admission. Patients will be excluded from enrolment if they are pregnant, admitted to the ICU solely for the purposes of palliative care or confirmation of brain death and/or have an advanced care directive or previously stated wish not to be included in research activities.

All eligible patients at participating sites will be included in this study under a waiver of consent in line with the National Statement (chapter 2.3) and NHMRC Ethical Considerations in Quality Assurance and Evaluation Activities, 2014. If the patient survives to hospital discharge, a study investigator will invite the patient or their surrogate decision-maker to participate in the 6-month telephone interview. An information brochure will then be provided offering the opportunity to opt-out of the follow-up interview. Interpreter services will be made available for participants and/or person responsible whose primary language is other than English.

Clinical management

Participants will undergo usual clinical care by their treating clinicians throughout their participation in the study. Clinicians will be permitted to view time series neuromonitoring data of ICP and CPP. This will allow clinicians to assess trends in monitored variables over time. Measures of cerebral autoregulation (Pressure Reactivity Index; PRx) and optimum CPP (CPPopt) will also be accessible but will not be used to guide clinical making as they are not standard of care in the Australian setting.

Data collection

Data from each of the following list of categories will be collected for all enrolled participants from hospital electronic clinical information systems by trained research staff. These data will include common data elements for TBI as identified by Maas *et al*²¹ and have been selected to balance data collection workload against comprehensive characterisation of injury and subsequent clinical management and outcome.

1. Demographics: age, gender, height, weight, frailty score, medical history (eg, previous TBI, smoking status, comorbidities) and social circumstances.
2. Injury characteristics: time of injury, mechanism of injury, location of injury, Injury Severity Score, Abbreviated Injury Score and International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) score.
3. Prehospital: vital signs and management including incidence of hypotension and hypoxia.
4. Process of care data: time to neurotrauma centre admission, time to CT scan, time to operating theatre, time to ICU and time to surgery, admission CT scan (Marshall and Rotterdam CT scores generated centrally from DICOM image files).
5. Admission clinical data: admission biochemical and haematological values, Glasgow Coma Scale.
6. Daily clinical data: therapeutic intensity level, sedation type, fluid balance and incidence and management of

neuroworsening,²² type and duration of venous thromboembolism prophylaxis.

7. High frequency clinical neuromonitoring data: ICP, CPP, PRx, CPPopt. These data will be collected continuously while the patient is in the ICU, with invasive neuromonitoring in situ.
8. Hospital discharge details: discharge destination and mortality.

For each participant, admission clinical data will be used to automatically calculate an IMPACT outcome prediction score within the REDCap database. Functional neurological recovery will be assessed using the GOSE questionnaire 6 months post-injury. Follow-up assessment will be performed over the phone by trained assessors, either from the ANZIC-RC, or using GOSE scores recorded in regionally based trauma registries (eg, Victorian State Trauma Registry).

A detailed data dictionary has been developed and provided to all participating sites. The data dictionary contains detailed definitions for each data variable, data source as well as the format of the data collected and instructions on how to handle missing data.

Data management

All patient data will be deidentified and assigned a unique study identification number. Data will be collected by trained research co-ordinators at each of the study sites and entered into electronic case report forms managed in REDCap,²³ an electronic data capture tool hosted by the Clinical Informatics and Data Management Unit Monash University. A trial master file containing recruitment logs will be securely stored at each site. Non-identifiable high frequency neuromonitoring data and brain CT images will be sent from participating sites to Monash University using a secure file transfer protocol.

Data handling and analysis

For all continuous neurophysiological measures, established methods will be first used to clean sensor data (eg, MAP, ICP, CPP) of artefacts. In this context, removal of artefacts is critical to improve downstream medical analyses and will use both supervised and unsupervised methods.^{24 25} The raw data will be manually curated to correct for known discrepancies. This includes but is not limited to date-time alignment with local time, change of signal sources, connection failure and unreliable signal. The manually curated data will then be down sampled, filtered and recalculated to generate trend data such as ICP burden per minute, which can be further summarised and standardised to longer periods (days since randomisation or full recording period). The total burden of intracranial hypertension (calculated as the area under the curve for ICP values > 22 mm Hg²⁶) and the treatments employed in individual patients, will be key initial parameters for investigation. The impact of variations in clinical care will be assessed against ICP control and 6-month functional outcomes. Institutional performance will be measured with reference to both established guidelines

(where available and of suitable quality) and consensus determined benchmarks of high-quality clinical management of msTBI. Deidentified between-site comparisons will also be completed and provided to sites to inform internal quality control and contribute to the 'learning healthcare system'.²⁷ Our statistical approach will use 6-month GOSE as the primary outcome, and exposure variables will be determined with reference to established guidelines (eg, maintenance of ICP < 22 mm Hg), literature reviews (eg, maintenance of euvolaemia) and a Delphi process for selection of benchmarks (eg, time to CT scan < 1 hours).

The primary outcome of an unfavourable GOSE at 6-months post-injury will be defined as a score of 4 or less on the 8-point scale. The midpoint, dichotomised GOSE will be modelled as a binomial random variable with a null hypothesis of equality between exposure groups in the proportion of subjects with a favourable outcome. This will be assessed with hierarchical binomial regression with patients nested within sites and sites treated as a random effect, applied to the full analysis set of patients. This primary outcome will be reported as the unadjusted risk ratio with associated 95% CI and as the risk difference with 95% CI and ORs with 95% CI. The number needed to treat for benefit or harm will also be reported if a statistically significant difference between exposure groups is demonstrated. All analyses will be adjusted for the baseline extended IMPACT TBI probability of a 6-month unfavourable outcome. These analyses will be undertaken by statistical support services within the ANZIC-RC.

As data collection and analysis are completed, individualised reports will be provided to all participating sites. Each report will provide detailed feedback on processes of care (eg, time to and duration of intracranial monitoring), adherence to established guidelines (eg, overall burden of intracranial hypertension per patient) and the degree of variability between centres. Individual institutional reports will be generated once complete data have been obtained for 20 patients at each site, with updates provided with each additional 20 patients. A report containing data from all sites summarising the epidemiology and clinical management of msTBI at a national level will also be provided to sites and the public via a lay summary.

Data sharing agreements

All named investigators will have the opportunity to identify areas of clinical equipoise in the management of msTBI, perform systematic reviews of the literature, design and implement research projects and access the data collected as part of PRECISION-TBI. If they fall within the remit of non-interventional studies covered by a waiver of consent, these projects may be included as substudies (subject to independent ethical approval). In the case of studies requiring an alternative consent model, these studies will be considered affiliate projects, requiring data sharing agreements in addition to independent ethical approval. Specific examples of affiliate

projects with data sharing agreements in principle are the PREDICT-TBI study²⁸ and the Artificial Intelligence-Enhanced Management of Severe TBI (AIMS-TBI)²⁹ studies. The PREDICT-TBI project aims to use advanced imaging techniques, blood-borne biomarkers and artificial intelligence (AI) techniques to accurately predict neurological outcomes, while the AIMS-TBI study focuses on the development and operationalisation of clinical AI algorithms designed to aid in the management of patients with mTBI in real time. Post hoc we plan to link the PRECISION-TBI database with other institutional and/or regional databases, so as to explore the impact of extracranial hospital-acquired complications on 6-month outcomes.

ETHICAL CONSIDERATIONS AND DISSEMINATION

Given the observational nature of the study and the inability of patients to consent to inclusion, participants will be enrolled under a waiver of consent, in line with the National Statement (chapter 2.3) and NHMRC Ethical Considerations in Quality Assurance and Evaluation Activities, 2014. In the event of survival to hospital discharge, the participant or their surrogate decision-maker will be offered the opportunity to opt-out of the follow-up interview and request removal from the study. These provisions were approved by The Alfred Human Research Ethics Committee (Alfred Health, Melbourne, Australia—project reference: 370-22)

The results of this research will be disseminated via original research articles in peer-reviewed journals and presentations at national and international conferences. Where possible publications will be open-access articles in order to maximise visibility of results. All publications that result from the PRECISION-TBI study using national data will include in the authorship designation: ‘on behalf of the PRECISION-TBI participants and investigators’. Requests to share data will be considered in accordance with institutional data sharing policies and where possible, deidentified data will be made available to independent investigators in accordance with the findability, accessibility, interoperability and reusability principles of data management and stewardship.³⁰

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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