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Predicting Outcome Following Mild Traumatic Brain Injury: Protocol for the Longitudinal, Prospective, Observational Concussion Recovery (*CREST)* Cohort Study

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Abstract

Introduction Mild traumatic brain injury (mTBI) is a complex injury with heterogeneous physical, cognitive, emotional and functional outcomes. Many who sustain mTBI recover within two weeks of injury, however, approximately 10-20% of individuals experience mTBI symptoms beyond this 'typical' recovery timeframe; known as persistent post-concussion symptoms (PPCS). Despite increasing interest in PPCS, uncertainty remains regarding its prevalence in community-based populations and the extent to which poor recovery may be identified using early predictive markers.

Objective 1) Establish a research database of people who have experienced mTBI and document their recovery trajectories; 2) Evaluate a broad range of novel and established prognostic factors for inclusion in a predictive model for PPCS.

Methods and analysis The Concussion Recovery Study *(CREST)* is a prospective, longitudinal observational cohort study conducted in Perth, Western Australia. *CREST* is recruiting adults aged 18-65 from medical and community-based settings with acute diagnosis of mTBI. *CREST* will create a state-wide research database of mTBI cases, with data being collected in two phases. *Phase I* collates data on demographics, medical background, lifestyle habits, nature of injury and acute mTBI symptomatology. In *Phase II*, participants undergo neuropsychological evaluation, exercise tolerance and vestibular/ocular motor screening, MRI, quantitative electroencephalography, and blood-based biomarker assessment. Follow-up is conducted *via* telephone interview at 1-, 3-, 6- and 12-months after injury. Primary outcome measures are presence of PPCS and Quality of Life, as measured by the Post-Concussion Symptom Scale and the Quality of Life after Brain Injury questionnaires, respectively. Multivariate modelling will examine the prognostic value of promising factors.

Ethics and dissemination Human Research Ethics committees of Royal Perth Hospital (#RGS0000003024), Curtin University (HRE2019-0209), Ramsay Health Care (#2009), and St John of God Health Care (#1628) have approved this study protocol. Findings will be published in peer-reviewed journals and presented at scientific conferences.

Trial registration number ACTRN12619001226190

Strengths and limitations of this study

- *CREST* is a prospective, longitudinal cohort study recruiting adult participants who have experienced mTBI *via* hospital emergency departments and community-based pathways in Perth, Western Australia.
- A primary strength of *CREST* is the establishment of a clinical research database of mTBI in Western Australia and documentation of variable recovery trajectories, for which there is currently limited data.
- Another asset of *CREST* is the investigation of novel and established pre-injury predictive factors, blood-based biomarkers, neuropsychological tests, exercise tolerance, vestibular/ocular function, and advanced neuroimaging outcome measures with the aim of generating a predictive model from this 'suite' of factors that may be useful for identifying individuals at risk of experiencing delayed recovery following mTBI.
- A primary limitation of this study may be loss to follow-up and resulting missing data points.
- Other limitations include possible selection bias on the basis of geographic location or injury severity, and sample-size constraints pertaining to predictive modelling.

Introduction

Mild traumatic brain injury (mTBI), also known as concussion, accounts for approximately 80% of all traumatic brain injuries occurring both in Australia and worldwide [1]. mTBI is characterised by a rapid, transient change in neurological function [2,3] accompanied by numerous signs and symptoms, the most frequent of which are headache, neck pain, dizziness, difficulty concentrating, and alterations in mood and sleep [4]. mTBI sequelae can be broadly classified into physical, cognitive, emotional and sleep-related domains [5], although the clinical presentation of mTBI is known to vary considerably between individuals [6], significantly hampering development of reliable prognostic tools.

The prevailing notion of mTBI recovery trajectory implies that symptomatic resolution can be expected within approximately two weeks of injury [7–10]. However, it is increasingly realised that recovery is complex and multifactorial [11], and this recovery trajectory which has been previously defined in the literature pertaining to young sportspeople may not necessarily reflect recovery across age, sex, and socioeconomic status. It frequently is cited that 10-20% of individuals who sustain a mTBI will experience symptoms at least 1 month following injury [12], known as persistent post-concussion symptoms (PPCS)[13]. Determining the true prevalence of PPCS has been complicated by the lack of consistent follow-up across studies and the non-specific nature of the condition [14]. The multitudes of documented ramifications stemming from PPCS have contributed to its status as an emergent public health issue. PPCS may profoundly impact an individual's ability to carry out activities of daily living, and can result in functional consequences including delayed or reduced ability to return to work [15,16],

study [17] and playing sport [18], as well as impaired satisfaction and quality of life [19–22]. Furthermore, PPCS has been linked with heightened use of healthcare services [23–25], making it an under-recognised economic burden.

It is not currently possible to identify which individuals will experience delayed recovery at the time of mTBI diagnosis, nor is there a consensus on how to manage patients who experience such a debilitating constellation of symptoms. The ability to predict who will develop PPCS would be of great benefit. From a clinical perspective, a prognostic model would assist with decision-making and management of patient expectations about their recovery. Importantly, it would enable the provision of personalised healthcare to patients by facilitating triage to the most appropriate forms of treatment according to individual needs *before* symptoms become chronic, thereby potentially resulting in improved patient outcomes. Researchers would also benefit from prognostic models, which could be utilised to enrich clinical trials for evidence-based treatments, which aim to prevent or ameliorate the effects of PPCS or other late-stage conditions associated with mTBI, such as Chronic Traumatic Encephalopathy [26–31] or Alzheimer's disease [32–34].

A plethora of studies have been conducted assessing biomarkers and other factors for their capacity to predict outcome following mTBI. However, variations in study methodologies have resulted in inconsistent results reported in the literature [35,36], and many of the studies conducted to date have been limited to investigating only one type or at best a small subset of prognostic factors [37]. Demographics and injury-related characteristics are amongst the most frequently examined variables, partly because of the convenience with which they can be extracted from medical records. Factors including female sex [38–41], previous history of mTBI [42,43], and pre-injury mental health issues [41,43–48] have all been flagged as potential predictors of PPCS, while others such as age [49], educational status [40,42,50], loss of consciousness [35,48,50,51] and (post-traumatic) amnesia [35,42,52–54] are contentious and require further and more thorough investigation. Reports of poor cognitive function following mTBI has led to the investigation of individual performance on neuropsychological tests as a potential predictor of PPCS. A heightened risk of PPCS has been found amongst individuals who perform poorly on post-mTBI tests of executive function [54], memory [38,55–57] and psychomotor function [53], however, the overall fidelity with which neuropsychological measures alone can prognosticate PPCS has been called into question given that individual performance can be influenced by extraneous factors such as age, prior education, and socio-economic status [58–61]. Consequently, efforts have turned towards identifying and examining other markers of PPCS. Blood-based biomarkers are one viable option that has been embraced by the research community, as they can be a relatively inexpensive and rapid way of assessing the physiological mechanisms that underpin conditions of interest. To date, a vast array of candidate biomarkers pertaining to cellular structural or functional damage as well as the biochemical and molecular

secondary injury cascades have been investigated for their ability to predict outcome after traumatic brain injury [62–64]. While biomarkers such as S100B [65] and the combination of glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) [66] have been proposed to assist with clinical decision making processes relating to traumatic brain injury, studies specifically assessing the relationship between fluid biomarkers and clinical outcome following mTBI have generally yielded small or variable effects [67]. More recently, a host of neuroimaging techniques (e.g. MRI [68], CT [69], PET [70]) and physiological biomarkers (e.g. exercise tolerance [71], vestibular/ocular function [72], psychomotor responses [73]) have also been identified as having the potential to serve as objective markers of PPCS, however, investigations into their prognostic capabilities have yielded inconsistent results and/or been relatively limited, and thus their utility remains to be ascertained. Similarly, the potential for personal predispositions (e.g. resilience [74], coping style [75]) to influence outcome following injury has also been acknowledged, but more research is needed to elucidate the extent of involvement.

Considering that a single predictive variable is unlikely to be the 'silver bullet' that predicts outcome at the level of the individual [35], it is not altogether surprising that research is yet to accurately identify which individuals will experience PPCS. It is increasingly recognised that a more fruitful approach would draw from multiple assessment elements for multivariate prognostic modelling to better calibrate the risk of poor clinical outcomes [35]. No study to date has successfully developed a prediction model that is targeted specifically for prediction of individual patient outcomes following mTBI [35,76]. Efforts to develop validated and pragmatic tools for use in a clinical and/or research context have been impeded by considerable variation between studies and use of suboptimal methodologies across studies [12,76]. Common limitations identified include small and/or selected sample sizes (often resulting from the use of a single centre), recruitment of participants beyond the acute injury period or across a wide post-injury timespan, inconsistencies in definition and measurement of PPCS as well as variable follow-up time points [35,76,77]. Furthermore, prognostic models arising from retrospective study cohorts often encounter additional issues including poor data quality, missing data, minimal use of validated symptom scoring scales, and lack of standardised acute evaluations [77].

The Concussion Recovery Study *(CREST)* is a large, cross-institutional study conducted in Perth, Western Australia (WA), developed with the aim of identifying individuals that are at an increased risk of developing PPCS. Approximately 2.4 million people reside in WA, of which 79% live within the capital city of Perth [78]; the most isolated capital city in the world. The greater Perth area extends a distance of over 125km, occupies an area of 6418 km^2 [79], and is served by 10 Emergency Departments (EDs: 1 private and 9 public, of which 1 is maternity and 1 is child/adolescent exclusively). *CREST* is collecting longitudinal data in two phases and utilises a multivariate, 'suite-based' approach that incorporates demographics, injury-related characteristics, neuropsychological assessment, blood-based

biomarkers, MRI, qEEG, exercise tolerance and vestibular/ocular function to develop an evidence-based acute predictive model for PPCS.

Objectives

The primary objectives of *CREST* are:

1. To establish a large-scale clinical research database of adults experiencing mTBI in Western Australia, in order to observe the typical pattern of recovery from mTBI and determine the incidence of PPCS.

2. To identify a suite of pre-injury factors and outcome measures during the early presentation period that may be used to predict those at risk of experiencing PPCS compared to those who recover within a typical timeframe.

The secondary objective of the *CREST* study is to:

1. Determine the feasibility of recruiting a large cohort of participants with mTBI from a variety of sources (e.g., EDs, general practitioners (GPs), and community sporting groups), as this widespread collection of community mTBI data has not previously been conducted to this scale in Australia or internationally to date.

Methods and Analysis

Patient and Public Involvement A *Community Conversation* was held in August 2018 involving clinicians and general community members with and without a history of mTBI. The conversation took form of a thematic exploration of current management considerations for mTBI, assessment measures, long-term prognosis and symptomatology and contributing factors to recovery. This public consultation highlighted the need for research to determine the predictors for poor outcomes following mTBI and growing interest in combining screening tools, radiological scans, and biological markers for predictive purposes. This stakeholder group shaped the design of the study by highlighting the importance of recruiting participants from the wider community, in addition to clinical populations. The clinicians shaped the *CREST* study's multimodal research design. Several individuals who participated in the *Community Conversation* assisted with recruitment strategies and dissemination of information, although there were not asked to assess the burden of the time required to participate in the research. Interested members of the group will be consulted at the conclusion of the study to guide dissemination of findings.

Study Population & Recruitment Criteria

CREST aims to capture a broad cross-section of community mTBI resulting from a variety of different injury mechanisms (e.g. assault, falls, sports, transport accidents, workplace incidents). Enrolment into *CREST* is open to individuals aged 18 to 65 years who have sustained a medically diagnosed mTBI within the last 7 days. Table 1 details additional inclusion and exclusion criteria for *Phase I* and *Phase II* of the study.

Table 1. Inclusion and Exclusion criteria for *Phase I* and *Phase II* of *CREST*

Phase I
Inclusion Criteria
• Aged 18-65 years • mTBI within 7 days • Diagnosed with mTBI by medical practitioner
Exclusion Criteria
• Significant history of pre-existing conditions that would interfere with outcome assessment and follow-up (e.g. substance abuse/alcohol abuse, homelessness, terminal illness) • Significant debilitating pre-existing diagnosed mental health disorder that would interfere with neuropsychological and possibly blood biomarker outcome measures, or ability to contact for follow-up (e.g. schizophrenia, bipolar disorder). • Significant pre-existing neurological condition, which may interfere with ability to complete outcome measures or follow-up (e.g. stroke, dementia) • Pre-existing cognitive impairment (e.g. intellectual disability), which may interfere with ability to undertake neuropsychological examination • Non-English speakers or individuals with poor English language skills • Prisoners in custody or people known to be involved in illegal activity • Head injury deemed to be entirely due to primary seizure • Pregnancy
Phase II
Inclusion Criteria
In addition to Phase I Inclusion Criteria • Willing and able to attend the Curtin University and Perron Institute for Neurological and Translational Sciences research tenancies located at the Ralph and Patricia Sarich Neuroscience Research Institute within 7 days of date of injury, and Sir Charles Gardiner Hospital for MRI within 9 days of injury.
Exclusion Criteria
In addition to Phase I Inclusion Criteria 1. Significant other physical trauma that would interfere with physical and/or biochemical outcome assessments and follow-up (e.g. lower limb injuries that would compromise balance or exercise bike testing, or cause changes in blood biomarkers) 2. Any pre-existing heart conditions or other medical conditions that may compromise ability to complete an exercise tolerance test 3. Epilepsy or history of seizure 4. Meets exclusion criteria to undertake MRI, which can be any of the following: a. Has cardiac pacemaker or pacing wire in situ b. Has metal surgical clips or staples of any kind (particularly aneurysm clips) in situ c. Has lap band surgery d. Has electronic inner ear implants (bionic ears) e. Has metal fragments in eyes (past or present) f. Has electronic stimulators g. Has implanted pumps h. Has metal pins or rods in bones i. Has an IUCD fitted j. Has shrapnel, bullets or foreign bodies k. Is pregnant l. Has braces m. Has embolization coils* n. Unable to lie flat*

*Note: *: item not strictly listed as an exclusion criterion but screened for as part of routine practice at the SCGH MRI Department.*

Participant Recruitment Pathways

Recruitment occurs across multiple pathways including major WA Health hospital EDs located throughout the Perth metropolitan area (see Figure 1), GPs, sports physicians, allied health professionals, community/amateur and semi-professional sporting clubs, as well as self-referral to the study.

Hospital ED Pathway

Staff at hospital EDs screen for individuals presenting with mTBI for eligibility. Individuals may be considered for *CREST* if they provide a description of an incident likely to have resulted in a mTBI, with accompanying symptoms that can be attributed to that injury as defined by the World Health Organisation [80]. Prospective participants must also describe at least one of the following, as described by the American Congress of Rehabilitation Medicine [3] and Theadom and colleagues [81].

1. Alteration in mental state at the time of the incident. If present, loss of consciousness must not exceed 30 minutes in duration.
2. Neurological symptoms (e.g. headache, dizziness, fogginess) that may or may not be transient.
3. Memory loss for events immediately before or after the accident. If present, the duration of Post-Traumatic Amnesia must be less than 24 hours.
4. No significant findings on acute brain CT scan, or CT scan not required/performed.

Following the identification of individuals that meet the above criteria, clinicians or research staff assist prospective participants to fill out a *Participant Referral Form* (PRF: see Supplementary Document 1), which contains the individuals' date of birth, date of injury and contact details. The PRF functions as a *permission-to-contact* form that permits the hospital to release the participants' contact details to the *CREST* research team. Completed PRFs are emailed or faxed through to a dedicated email address, and *CREST* research team members then use a dedicated mobile telephone number to contact participants within 7 days following the date of injury noted on the PRF.

Community Pathways

In addition to recruiting individuals from Hospital EDs, *CREST* is also recruiting from the general community. The community-based pathway can be broadly categorised into the following three recruitment streams: *i) General Practitioner (GP)/sports physicians and allied health professionals*, *ii) Community Sports Groups* and *iii) Self-Referral*. Recruitment of prospective participants *via* the community pathways largely mirrors that of the hospital ED pathway.

GPs, sports physicians and allied health professionals

Private GP practices, sports physicians and allied health professionals within the Perth metropolitan area have been informed about the *CREST* study, either by direct in-person approach or by digital

communication (e.g. advertisement in professional association newsletters/mailing lists, social media). In this pathway, medical practitioners screen for individuals meeting the above criteria presenting at their practices. Details of interested participants are forwarded *via* email or fax to the *CREST* Research Team using the PRF.

Community Sports Groups

Physiotherapists, athletic trainers and medics at sports clubs approached by the *CREST* research team screen for prospective participants using the aforementioned criteria. If a player experiences a suspected mTBI at training or game day, they are informed of the *CREST* study by the attending first aid personnel, who provide the prospective participant with a copy of the PRF and direct them to seek medical confirmation of mTBI. Should they receive a diagnosis of concussion and wish to participate in the study, individuals can self-refer to the study by contacting the *CREST* Research Team themselves *via* telephone, email or website (https://concussionstudy.com.au/), or by requesting their attending medical professional to forward the PRF to the *CREST* research team on their behalf.

Self-Referral

Individuals from the general community who have sustained an mTBI may participate in the study *via* self-referral, and can do so by directly contacting the *CREST* Research Team *via* telephone, email, fax or website. Individuals recruited using this pathway are asked to provide the name of the medical professional who diagnosed them with an mTBI. In the event that prospective participants have not yet sought medical attention by the time they make contact with the research team, individuals are requested to first seek medical confirmation of mTBI. If prospective participants are able to meet this request and make contact with the research team within 7 days of date of injury, they remain eligible for study enrolment.

Study Design

CREST is a prospective, longitudinal observational cohort study, which follows participants over the course of one year after their mTBI. Individuals who do not develop PPCS serve as controls, which is in line with the study's second primary objective of identifying factors that may be able to discriminate between individuals who do and do not follow a typical recovery trajectory following mTBI. The study comprises of two parts, referred to as *'Phase I'* and *'Phase II'*, respectively, and follow-ups conducted at multiple time points. See Figure 2 for graphical depiction of study design.

Phase I

Phase I comprises a telephone interview, which is conducted within 7 days of date of injury. During this telephone call, information pertaining to demographics, injury-related characteristics, acute post-

mTBI clinical care, and medical background, exercise habits and experience of mTBI symptomatology is collected. *Phase I* typically takes 30 minutes to complete. This includes time required to explain the aims and procedures of the study and acquire verbal consent over the telephone, all of which take place prior to collection of data from the participant. Further detail about the data acquired in *Phase I* can be found in Table 2 below.

Phase II

Phase II has been designed to serve as a comprehensive in-person battery of tests, which is also completed within 7 days of date of injury. Testing takes place at the Curtin University and Perron Institute for Neurological and Translational Science, which are both located on the Queen Elizabeth II Medical Centre (QEIIMC) campus in Nedlands (Perth, Western Australia). During this session, qEEG is performed, a blood sample is taken, and neuropsychological, exercise tolerance and vestibular/ocular function testing is conducted. *Phase II* testing typically takes 2.5-3 hours to complete.

MRI is also performed as part of *Phase II* testing. This takes place at the Department of Radiology at Sir Charles Gardiner Hospital located on the QEIIMC campus. Due to the scheduling requirements of the scanner that is being utilised for the purposes of the study, the MRI is often performed separately to the other *Phase II* components, generally taking place afterhours or on weekends. To accommodate for scanner availability, *CREST* participants may be scanned up to 9 days following the date that they sustained their mTBI.

Follow-Up

Regardless of whether participants opt to complete *Phase I* only, or both *Phase I* and *Phase II*, they are followed-up by telephone interview at 1, 3, 6 and 12 months post-injury. To ensure consistency with follow-up timeframes, the following variations are being adhered to:

- 1 month follow-up is completed at 30 days +/- 4 days from date of injury
- 3 month follow-up is completed at 90 days +/- 7 days from date of injury
- 6 month follow-up is completed at 180 days +/- 14 days from date of injury
- 12 month follow-up is completed at 360 days +/- 30 days from date of injury

The purpose of the follow-up telephone interviews is to document each participant's recovery experience following their mTBI. Thus, at each follow-up time point, information is collected about the individual's return to physical activity, sport, work, and study (if applicable). During the follow-up telephone interviews, participants are also queried about whether or not they have *i)* received or are currently seeking any ongoing allied health, alternative or medical treatments for their mTBI (e.g. physiotherapy, psychotherapy, chiropractic or other medical treatment), *ii)* been diagnosed with a

migraine disorder subsequent to the mTBI, and *iii)* sustained another mTBI since the injury that they were enrolled in the study for. Furthermore, the participant's experience of ongoing mTBI symptomatology is ascertained using the *Post Concussion Symptom Scale-22 Item version (PCSS)* [82,83] at each follow-up time point, whilst quality of life is being measured using the short form of the *Quality of Life after Brain Injury* (QOLIBRI-OS:[84]) at the 3-, 6-, and 12-month follow-ups.

Data collection: *Phase I*

In *Phase I*, a semi-structured interview is conducted *via* telephone to collect data on participant demographics, circumstances of injury, acute post-mTBI clinical care, medical background, exercise habits and experience of acute mTBI symptomatology. This information is collected using a combination of custom-designed metrics and validated instruments (see Table 2).

Table 2. *Phase I* semi-structured telephone interview/questionnaire components

***Phase I* Telephone Interview/ Questionnaire Components**	
Demographics	Age, sex, height, weight, contact details, next of kin, nominated GP, highest level of completed education
Circumstances of Injury	Description of mechanisms of injury (e.g. sport, non-sport), whether other injuries were sustained during the incident resulting in the mTBI, compensation/litigation status, site/s of impact, loss of consciousness (presence/absence, duration), amnesia (presence/absence, nature: anterograde and retrograde, duration), experience neck pain, presence of seizures or fits following the mTBI, estimated amount of alcohol consumed prior to incident (in standard drinks)
Acute post-mTBI Clinical Care	Details of where medical attention was sought (i.e. ED, GP, First Aid personnel), CT scan performed or not.
Medical Background	Number of previous concussions, including the date and duration of recovery for the most recent concussion, previous whiplash injury (how many in total, date of most recent); whether participants have ever been diagnosed with epilepsy, seizure disorder, migraine or other headache disorder, mental health disorder, sleep disorder, learning disorder: for each of these health conditions, participants are also asked whether they are currently receiving treatment for this disorder (namely, medication and dosage), whether they take prescribed medication on a regular basis (i.e. anti-inflammatory, blood thinners, pain medication, other)
Exercise Habits	Exercise on a regular basis (number of times per week, type of exercise: strength training, cardiovascular exercise, sport)
Acute mTBI symptomatology	*PCSS*

Data Collection: *Phase II*

qEEG

EEG data acquisition and analysis EEG acquisition is conducted using a 19-channel Electro-cap (Electro-Cap International Inc., Eaton, Ohio: USA) and a Mitsar amplifier (Mitsar, Ltd., St Petersburg, Russia), with quantitative and low resolution electromagnetic tomography analysis (LORETA) conducted using NeuroGuide software (Applied Neuroscience, Inc., Florida, USA), which has been extensively validated in the literature, including within populations with mTBI [85,86]. For scalp EEG recording, the participant's head circumference is measured and fitted with an appropriately sized Electro-cap, with all electrodes connected using the standard 10-20 system (See Supplementary Figure 1). Each scalp electrode is prepared by parting the hair and filling it with electroconductive gel (Electro-Gel™, Electro-Cap International Inc, Eaton, Ohio: USA). EEG activity is recorded from 19 scalp electrodes and impedance kept below 10 kΩ, using a linked ears montage, where the ear lobes act as a reference. Resting state data is recorded for 10 minutes, with five-minute eyes open and eyes closed condition blocks. Approximately 60 seconds of artefact-free data will be selected using NeuroGuide software (Applied Neuroscience, Inc.), and individual's activity will be compared to the software's normative database (N = 727). This comparison will provide a Traumatic Brain Injury Index score using a TBI Discriminant Index [86], indicating the severity of the person's TBI ranging from zero to ten (normal = 0, mild = 1 to <3, moderate = 3-5, severe = >5). LORETA analysis and NeuroNavigator software (Applied Neuroscience, Inc., Largo, Florida: USA) will be used to identify areas of dysfunction within networks of interest.

Blood-Based Biomarkers

Blood sample collection and analysis Trained research assistants obtain a 20mL blood sample from non-fasting participants by venepuncture. Whole blood is collected into BD Vacutainer® ethylenediaminetetraacetic acid (EDTA) and serum (SST) blood collection tubes, and rested at room temperature for approximately 30 minutes before centrifugation at 3000 rpm for 10 minutes at 4°C. Samples are then aliquoted into 250 μL vials and put into long-term storage at -80°C until analysis. Blood samples will be analysed by a variety of methods with the intent of quantifying novel and established fluid biomarkers that are associated with mTBI pathophysiology. In particular, protein biomarkers pertaining to neuronal and glial structure and function (e.g. GFAP, UCH-L1), mircroRNAs, genetic signatures, phenomics and metabolomics will be investigated. An additional whole blood sample is examined using a haematology panel (Mindray BC-2800 Vet Auto Hematology Analyzer; Shenzhen, China) to investigate differences in blood components.

Neuropsychological Assessment and Questionnaires

Participants undergo a brief neuropsychological assessment, which is conducted by trained research team members who have a postgraduate qualification in psychology, under the supervision of a clinical neuropsychologist (CP). The ability to assess a broad range of cognitive domains and executive functions known to be affected by mTBI in a timely manner was the primary driver for the selection of tests comprising the neuropsychological testing battery. More specifically, the *Repeated Battery for the Assessment of Neuropsychological Status Update (RBANS® Update)*[87] is being used to measure immediate and delayed memory, visuospatial constructional skills, language and attention, while the *Trail Making Test Forms A* and *B* [88] are being used to measure components of executive function. Effort is also measured using the *Rey Memory Test* [89]. In addition, participants complete a battery of questionnaires to assess mTBI symptomatology (*PCSS)*: [82,83]), psychological distress (*Depression Anxiety and Stress Scales-21 item version*: [90], and *Brief Symptoms Inventory-18 item version* [91]), resilience (*Brief Resilience Scale*: [92]) and coping style (*Utrecht Coping List*: [93,94]). The neuropsychological assessment and questionnaires are both completed in a private room, and in accordance with standard neuropsychological testing arrangements, with administration time typically taking 30-40 minutes. Diagnosis of PPCS will be made on the basis of a moderate-to-severe score on the *PCSS* scale in line with best practice guidelines.

Buffalo Concussion Bike Test

Participants undergo exercise tolerance testing using the *Buffalo Concussion Bike Test (BCBT)* as outlined by Haider and colleagues [95] which involves graded exertion on a recumbent bicycle ergometer (Monark RT2, Monark Exercise, Vansbro, Sweden). Prior to conducting the test, participants are screened using the *Physical Activity Readiness Questionnaire (PAR-Q)* [96] to assess for pre-existing cardiac issues or increased risk for cardiopulmonary disease, orthopaedic issues or injuries that may limit their ability to cycle, as well as other medical issues that may impede their ability to complete the exercise test safely. Participants are then asked to rate their current symptoms at rest on a 0 to 10 point visual analogue scale (VAS), and the test is not conducted if their score is 5/10 or more at rest. Heart rate (HR) at rest is determined after five minutes of quiet sitting using a Polar OH1+ armband (Polar Electro Oy, Kempele, Finland). During the test, the participant is asked to maintain a set workload as calculated by a pre-determined formula based upon body weight [95]. Exercise intensity is increased every two minutes by increasing the required workload. HR, rating of perceived exertion (RPE) and symptom exacerbation are also monitored and documented at the end of each stage. RPE is determined using a modified Borg scale, which records an individual's subjective level of exertion on a scale of 6 to 20 [97], and symptom levels on a VAS of 0 to 10 are also recorded. The criteria for ceasing the test include: *i)* symptom exacerbation of more than two points from the pre-exercise value (including an increase in current symptoms or the appearance of a new symptom), *ii)* voluntary exhaustion as ascertained by a RPE exceeding 17, *iii)* judgement by the researcher that the participant

is displaying visible signs of distress, or *iv)* a request by the participant to stop the test. The participant's HR at cessation of the test is recorded as the 'HR threshold'.

Vestibular/Ocular Motor Screening (VOMS) Assessment

The VOMS assessment is a targeted test used to identify vestibular and/or ocular motor dysfunction following mTBI as described by Mucha and colleagues [98]. Briefly, the VOMS involves examining horizontal and vertical smooth pursuits, horizontal and vertical saccades, near point convergence (measured in centimetres), and visual motor sensitivity. Symptoms (namely headache, dizziness, nausea and fogginess) are monitored prior to the commencement of the test, as well as after the completion of each task, to determine the effect of each component on symptom exacerbation. Symptoms are recorded as a score on a VAS ranging from 0 to 10, and the test is ceased if symptoms increase by three points. Any abnormal findings or provocation of symptoms is considered a 'positive' test, and a potential indicator of vestibular/ocular system dysfunction. The *VOMS* takes approximately 5-10 minutes to complete.

Magnetic Resonance Imaging (MRI)

MRI Acquisition. MRI is conducted using a Philips Ingenia 3T Multi Transmit Wide Bore Scanner (Philips Healthcare, Best, The Netherlands) equipped with a 32-channel head coil. The imaging protocol takes approximately 50 minutes to compete and comprises standardised sequences as outlined in Table 3.

Table 3. List of *CREST* MRI sequences and their associated purpose

Sequence	Purpose
T_1- weighted magnetisation-prepared rapid gradient echo (MPRAGE)	Gray and white matter morphometry Anatomical reference
Susceptibility Weighted Imaging (SWI)	Quantitative Susceptibility Mapping (QSM)
Resting state functional magnetic resonance imaging (rs-fMRI)	Brain connectivity Correlation with qEEG findings
Pseudo-continuous Arterial Spin-Labelling (pcASL)	Cerebral blood flow
Diffusion Weighted Imaging (DWI)	White matter microstructure

MRI Data Analysis. Custom-built automated data processing pipelines will be constructed in Python under the Nipype framework [99] on Linux (Ubuntu 18.04 Bionic Beaver distribution) and deployed using Jupyter Notebook [100]. Raw DICOM data are concerted to NIfTI format and stored for analysis according to the Brain Imaging Data Structure (BIDS; [101]) recommendations.

Brain morphometry

T1-weighted data will be processed using Freesurfer image analysis software (http://surfer.nmr.mgh.harvard.edu/), from which volumetric and cortical thickness measurements will be extracted. Data may also be explored using voxel-based morphometry via SPM12 (https://www.fil.ion.ucl.ac.uk/spm/) in MATLAB (The MathWorks, Inc., Natick, Massacheusetts: USA).

Quantitative Susceptibility Mapping

SWI images will be preprocessed for QSM using the MEDI toolbox (http://pre.weill.cornell.edu/mri/pages/qsm.html) in MATLAB. This preprocessing toolbox includes removal of phase inconsistencies, estimation of frequency offset, phase unwrapping, and background field removal using projection onto dipole fields, followed by Morphology enabled dipole inversion (MEDI). Reconstructed QSM images will be explored for iron and calcium concentration using a region of interest (ROI)-based approach.

Resting state functional MRI

Images will be preprocessed using ANTS, FreeSurfer, SPM and aCompCor. Standard preprocessing methods will be employed, including despiking, slice time and motion correction, spatial normalisation to the MNI template, temporal normalisation, linear regression and bandpass filtering. Data will be explored using network connectivity and graph theoretic analysis.

Pseudo-continuous Arterial Spin Labelling

pCASL images will be used to quantify cerebral blood flow (CBF) using the BASIL toolkit in FSL (https://asl-docs.readthedocs.io/en/latest/index.html), with preprocessing including kinetic-model inversion using a Bayesian algorithm, calculation of the magnetization of arterial blood, and registration to MNI space. Data will be probed for both global and ROI-based analyses of CBF.

Diffusion MRI

Diffusion MRI image preprocessing will leverage FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl) and MRtrix software, with a pipeline including skull stripping, Gibbs deranging, correction for motion and eddy currents and susceptibility artefacts and bias field correction. Constrained spherical deconvolution will be used to estimate the white matter fibre Orientation Distribution Function. Outputs will be registered to MNI space for voxel-based exploration of white matter alteration via tract-based spatial statistics (TBSS; [102]) alongside ROI-based analysis for diffusion MRI metrics.

Clinical notification: All MRI scans are reported by a neuroradiologist with medically relevant incidental findings communicated to the participant's nominated GP.

General Data Management Plan

CREST's study design requires data collection using various media, including electronic and paper formats. Data acquired electronically (e.g. *Phase I* telephone interview) are being entered directly into a secure, encrypted REDCap® [103,104] database hosted by Curtin University. Paper copies of participant's personal information (e.g. PRF, results from *Phase II* components) are stored securely in a locked filing cabinet at the research office, and are also digitised and uploaded to REDCap® for storage. Imaging data (i.e. qEEG, MRI) are being organised according to the BIDS and are stored on a secure, cloud-based storage platform also provided by Curtin University, as well as on securely stored physical hard drives for long-term storage.

Upon enrolment into the study, all participants are assigned a unique identification number, and all data that are collected from participants are identified by this number. A master list containing select identifying information is securely stored on an encrypted server, and is available only to authorised research staff. All identifiable information accrued for the purpose of the research study is treated as strictly confidential, and will only be disclosed with permission from participants or as required by law. In line with WA Health guidelines, all research data will be retained for at least seven years.

Data Analysis Plan

This is the first registry of its kind in WA. As such there is no existing data from which to extrapolate power for calculations. Baseline characteristics will be compared using Chi-square tests for categorical variables and t-tests for continuous variables, with respect to outcome (PPCS or no PPCS). Standard regression modelling will be used to build best-performing prediction models for each of the outcomes of interest, using principal component analysis to identify the most promising predictive indicators to include in the model. Multiple measures of model performance, including calibration and discrimination as well as novel measures employing reclassification tables and net reclassification improvement will be used to establish the best and most parsimonious prediction model.

Ethics and Dissemination

Ethics approval for the study has been directly obtained from the Human Research Ethics Committees (HRECs) at all of the institutions involved in the study, or where applicable, reciprocal approval has been granted. Informed verbal consent is obtained from all participants over the telephone as part of

enrolment into the study, before data is collected in *Phase I*. Participants are provided with a copy of their verbal consent and study information documentation *via* email following the *Phase I* interview. Written consent is also sought from those participants partaking in *Phase II* prior to the undertaking of any testing components. All data and samples are managed entirely anonymously with the exception of the required information for follow-up telephone calls. There are few significant risks to the participants in this study, and for those that have been identified, appropriate protocols have been devised which have been approved by the HRECs. Participants can withdraw from the study at any time and this will not have any impact on their clinical care. Data contributed to the study can also be withdrawn upon request. The results of this study will be published in peer-reviewed journals and presented at local, domestic and international scientific meetings. No identifiable information will be published, unless permission has been obtained from participants to do so.

Discussion

Relative to studies previously conducted in the field, two main advantages distinguish the *CREST* study by design to provide superior insight into the recovery trajectory of individuals sustaining an mTBI. First: *CREST* is recruiting widely from a number of different clinical and community-based sources, with scope to recruit from regional/rural and remote areas in future. Not only will this facilitate the simultaneous observation of recovery trajectories associated with a variety of different mTBI injury mechanisms, but it will also provide insight into whether some factors may be more salient for recovery following mTBI due to different causal mechanisms. This unique recruitment approach will also provide much needed data regarding the circumstances under which mTBI occurs within WA as well as the incidence and prevalence of both mTBI and PPCS that may ensue, for which data is severely limited. Second: *CREST* utilises an extensive testing battery that comprises a broad range of both novel and established predictors of PPCS. This in itself is significant for several reasons: First and foremost, such an approach will enable the evaluation of previously identified factors in a novel, community based cohort that has been followed-up over a prolonged period of time. Furthermore, it features several novel techniques (e.g. QSM, qEEG, metabolomics, proteomics) that have received limited attention and others (e.g. exercise tolerance) that have been investigated only in specific populations (e.g. adolescent athletes), expounding the utility of such methods. The systematic approach adopted by *CREST* in which data is being collected also creates a fertile setting for the examination of novel or poorly investigated relationships between different clinical parameters predictive of poor outcome (e.g. congruency between qEEG and rs-fMRI; ASL and exercise tolerance), and provides opportunity for economic evaluation of diagnostic and prognostic methods from both the healthcare and consumer perspectives. Taken together, this research has the potential to empower clinicians and researchers alike by identifying factors that may contribute to the development of an optimal 'suite' of rapidly deployable predictive variables for the early identification of PPCS risk. It also has the potential to assist with the

early identification of patients at risk of experiencing PPCS and enable timely patient-centred treatment, and thereby help to reduce the personal, economic and societal burden of mTBI.

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Authors' contributions MF DF CP MB ML SZ DX conceptualised the study and participated in initial study design, with assistance from AG JT ET FB AvH. AG, SCH, JT, FB and MF drafted the manuscript. AG prepared visual content and coordinated manuscript revisions. MF DF CP MB ML SZ DX obtained the research funding. All other authors (ET SM AR GA BS SvS PB JI TC DX SR SH GC ML MB CP DF) contributed to study design and revisions of the manuscript.

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Competing Interests None declared.

Patient consent for publication Not required.

Ethics Approval This study protocol has been approved by the Human Research Ethics committees of Royal Perth Hospital (#RGS0000003024), Curtin University (HRE2019-0209), Ramsay Health Care (#2009), and St John of God Health Care (#1628).

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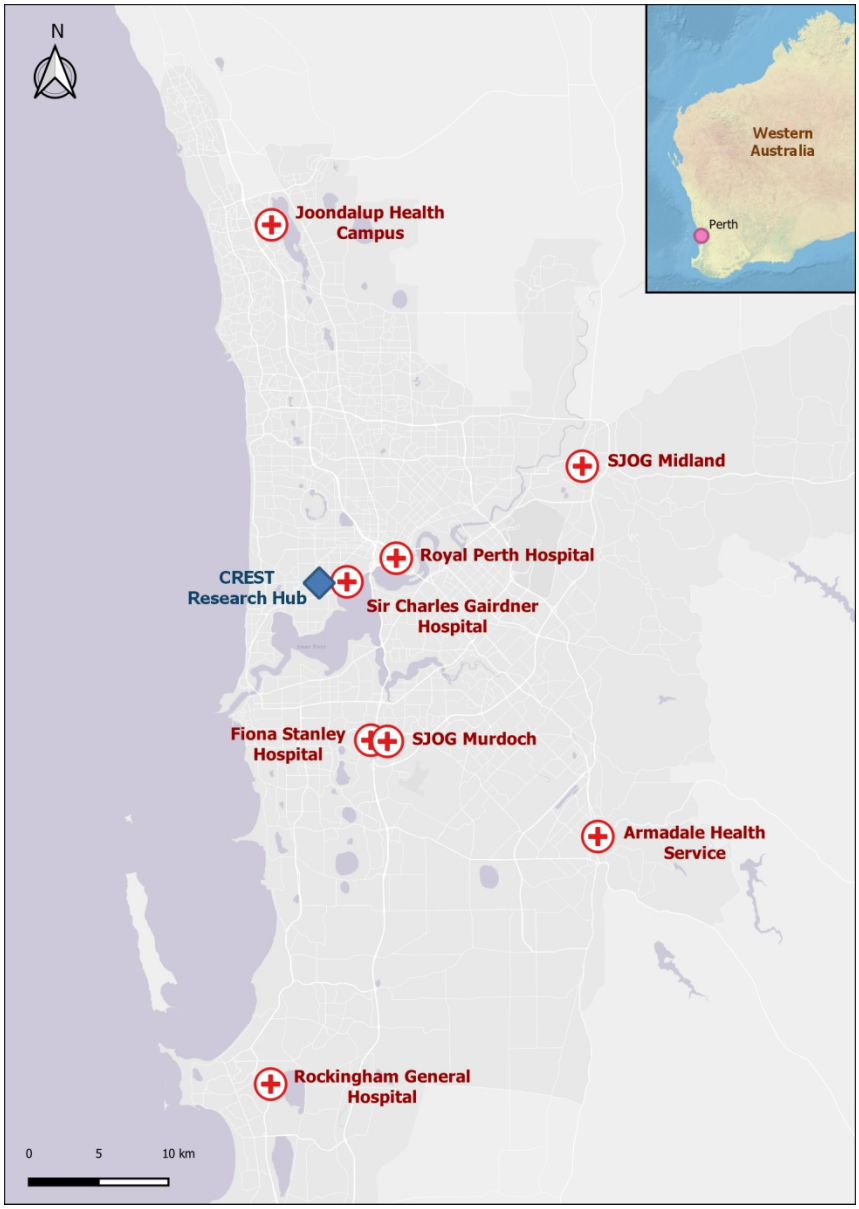
Figure Legends

Figure 1. Map showing location of hospital emergency departments (red crosses) throughout the Greater Perth Area from which prospective *CREST* participants are recruited, relative to the location of the *CREST* Research Hub (blue diamond). *Note:* SJOG: Saint John of God Hospital

Figure 2. Flow diagram of the *CREST* study design. Participants are recruited *via* Hospital ED or Community-Based Pathways using a dedicated *Participant Referral Form*. Following the receipt of a completed *Participant Referral Form*, either by email or fax, a member of the *CREST* research team uses a dedicated mobile telephone number to contact prospective participants. During this phone call, interested participants are briefed on the study aims and procedures, and verbal consent is obtained to participate in the study. Following this, the *Phase I* semi-structured telephone interview is conducted and upon its conclusion participants are asked if they also wish to participate in *Phase II* of the study. If interested, the *CREST* research team member completes a telephone screen to assess the participant's eligibility to undertake the additional components of *Phase II*. If a participant is deemed eligible, a testing session is organised at the *CREST* Research Hub. Both *Phase I* and *Phase II* components are conducted within 7 days of a participant sustaining an mTBI. All participants are followed-up by telephone interview at 1-, 3-, 6- and 12-months following the date of injury. *Note:* * Comprises the Curtin University and Perron Institute for Neurological and Translational Science tenancies, which are located at Queen Elizabeth II Medical Centre, Nedlands (Perth, Western Australia); †: MRI may be conducted up to 9 days following participant's mTBI; ‡: Quality of Life is assessed using the QOLIBRI-OS at 3-, 6- and 12-month follow-ups only. Abbreviations: EDs: Emergency departments; GPs: General practitioners; MRI: Magnetic resonance imaging; mTBI: mild traumatic brain injury; NPA: Neuropsychological assessment; qEEG: Quantitative electroencephalography; VOMS: Vestibular/Ocular Motor Screening test; WA: Western Australia.



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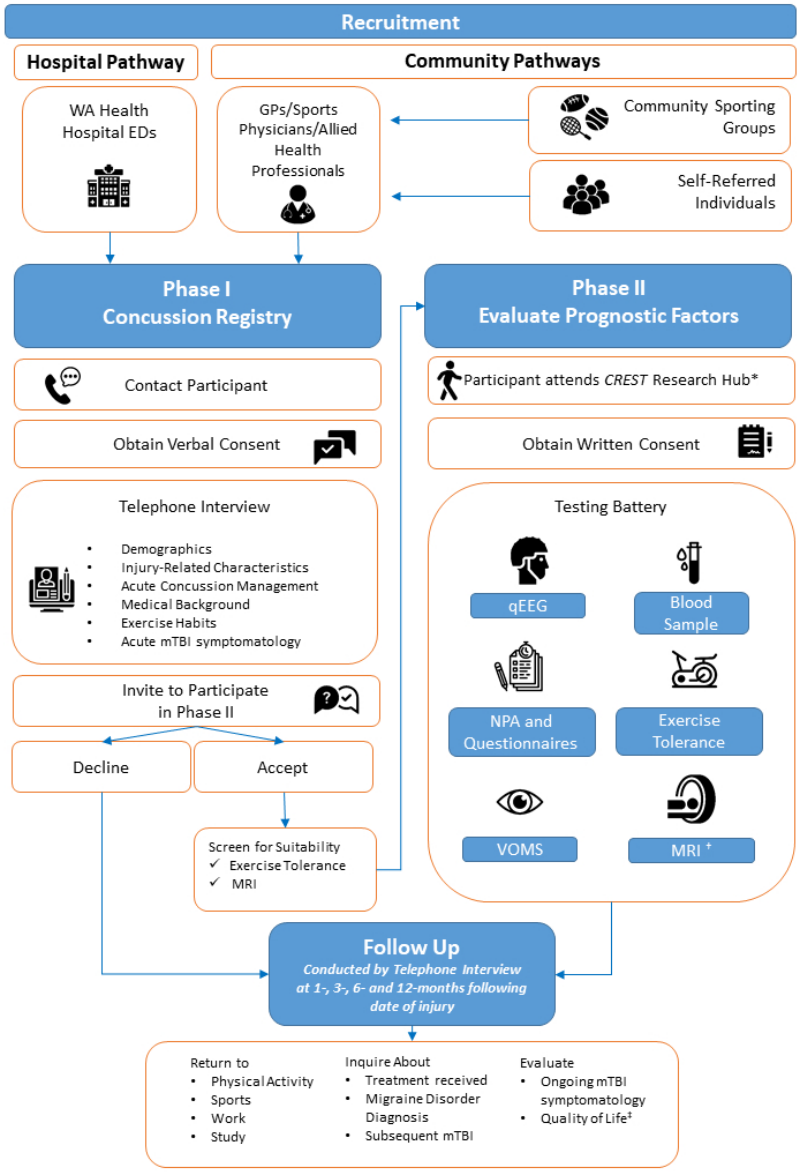

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Predicting Outcome Following Mild Traumatic Brain Injury: Protocol for the Longitudinal, Prospective, Observational Concussion Recovery (*CREST)* Cohort Study

Gozt, AK et al.

Supplementary information

1. Document 1. Participant site referral form.
2. Figure 1. The 10-20 International system of EEG electrode placement.
3. Table 1. MRI scan parameters.

Supplementary Document 1. Participant referral form

CURTIN HEALTH INNOVATION RESEARCH INSTITUTE | Curtin University | perron institute for neurological and translational science

CREST Concussion REcovery STudy

Participant Referral Form

Patient Name: **DOB: / /**

Phone: **Date of Injury: / /**

Email:

I consent to _____ (*Name of Healthcare Provider*) providing my details above to the Concussion Study team and to a member of that team contacting me to discuss the Concussion Study in more detail.

Patient Signature: **Date:**

MEDICAL PRACTITIONER TO COMPLETE THIS SECTION

Referring Doctor or Healthcare Provider Details

Name:

Practice Details or Stamp:

Signature: **Date: / /**

Key Participant Selection Criteria:

Identifying potential participants: To determine if a concussion has occurred, potential participants may be considered for this study if they provide a description of an incident likely to lead to a traumatic brain injury, with accompanying neurological signs and symptoms which can be attributed to that injury, as defined by the World Health Organisation. Participants must also describe **at least one** of the following, as described by the American Congress of Rehabilitation Medicine and Theadom and colleagues:

1. Any period of loss of consciousness (Were you "knocked out")?
2. Alteration in mental state at the time of the accident (Were you dazed, disoriented or confused? Did you "see stars" at the time of injury?)
3. Any memory loss for events immediately before or after the accident (Do you have any memory loss around the time of injury - before or after?)
4. Any focal neurological deficits (eg headache, dizziness, fogginess) that may or may not be transient?

Please forward the completed form to:

concussionstudy@curtin.edu.au

or

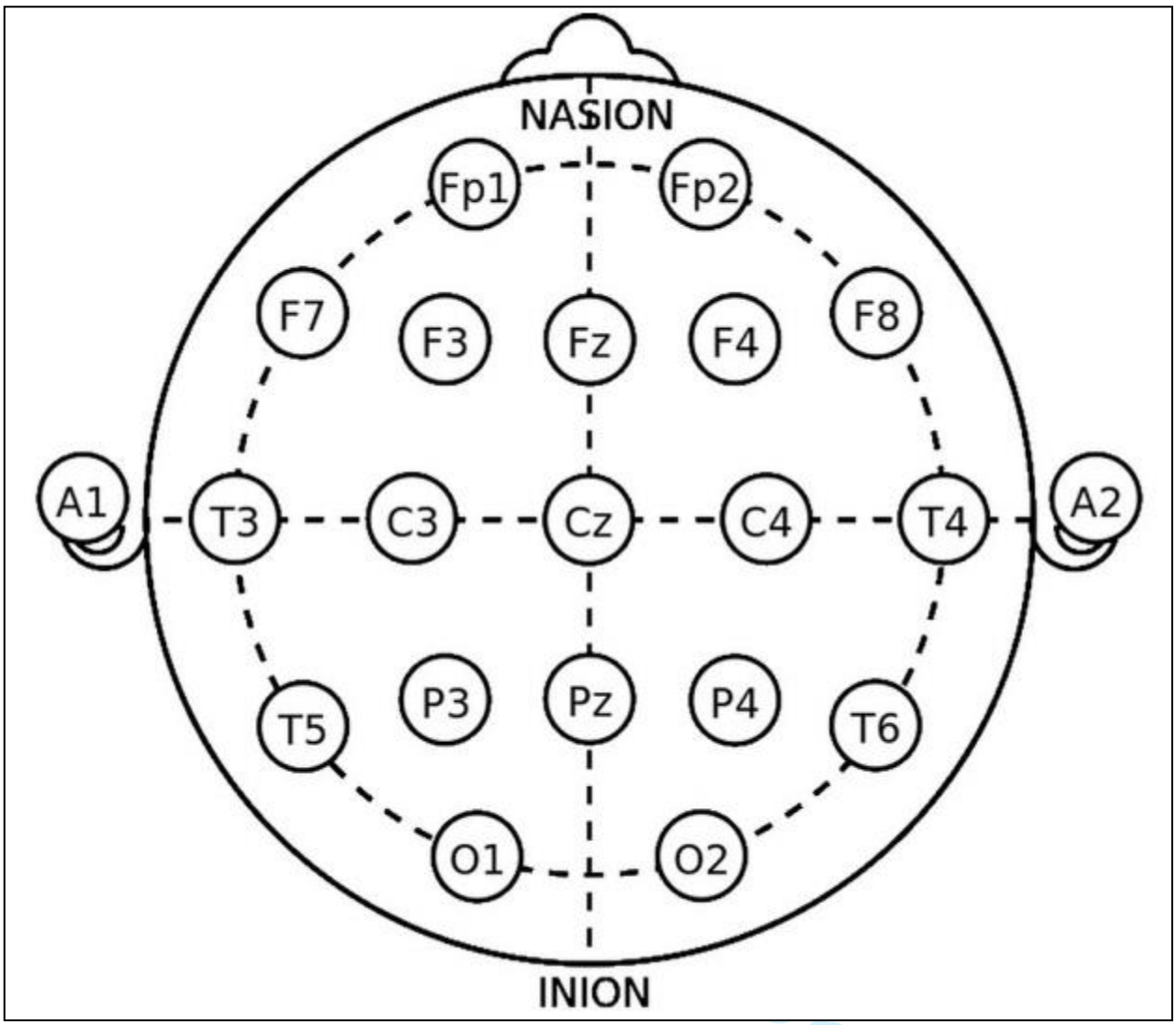
Secure e-fax 08 6270 5470

Thank you very much for your participation!

This study has Ethics Approval through Royal Perth Hospital Human Research Ethics Committee (#RGS0000003024) and Curtin University (HRE2019-0209). Please contact the Curtin research team on 0466 526 849 if you have any further questions.

Master Participant Referral Form V4 06/02/2020

Supplementary Figure 1. The 10-20 International system of EEG electrode placement.



Note: Figure adapted from Rojas G, Alvarez C, Montoya C, et al. Study of resting-state functional connectivity using EEG electrodes position as seed. *Front Neurosci*;12 doi:10.3389/fins.2018.00235 [published Online First 24 April 2018]

Supplementary Table 1. MRI scan parameters.

Sequence	T1	3D FLAIR	3D SWI	rs-fMRI	pCASL	DTI
Orientation	Transverse	Sagittal	Transverse	Transverse	Transverse	Transverse
Voxel size (mm)	1 x 1 x 1	1 x 1 x 1	0.7 x 0.7 x 1.4	3 x 3 x 3	3.75 x 4 x 8	2 x 2 x 2
TR (ms)	6.01	4,800	33.4	3,000	4,064	4,694
TE (ms)	2.7	302	5/4 echoes Δ7.7	30	11.17	113
TI (ms)	-	1600	-	-	-	-
Flip angle (deg)	8	90	10	90	90	90
Phase FOV (mm)	256	182.5	220	216	240	224
Matrix size	256 x 256	252 x 252	301 x 301	69 x 69	88 x 88	110 x 110
# slices	175	365	110	46	15	60
Fat suppression	no	no	no	yes	yes	yes
b-values (sec/mm^2) [directions]	-	-	-	-	-	0, 1500 [32]
Time (min)	6:19	3:31	9:40	7:42 [a]	4:45[b]	11:36

Note: [a]: 150 dynamics; [b]: Post-label delay 1800ms

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Predicting Outcome Following Mild Traumatic Brain Injury: Protocol for the Longitudinal, Prospective, Observational Concussion Recovery (CREST) Cohort Study

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Radiology and imaging, Neurology, Mental health, Evidence based practice
Keywords:	Neuroradiology < RADIOLOGY & IMAGING, MENTAL HEALTH, Neurobiology < NATURAL SCIENCE DISCIPLINES, Neurological injury < NEUROLOGY, NEUROLOGY, Neuropathology < PATHOLOGY

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Predicting Outcome Following Mild Traumatic Brain Injury: Protocol for the Longitudinal, Prospective, Observational Concussion Recovery (*CREST)* Cohort Study

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Abstract

Introduction Mild traumatic brain injury (mTBI) is a complex injury with heterogeneous physical, cognitive, emotional and functional outcomes. Many who sustain mTBI recover within two weeks of injury, however, approximately 10-20% of individuals experience mTBI symptoms beyond this 'typical' recovery timeframe; known as persistent post-concussion symptoms (PPCS). Despite increasing interest in PPCS, uncertainty remains regarding its prevalence in community-based populations and the extent to which poor recovery may be identified using early predictive markers.

Objective 1) Establish a research dataset of people who have experienced mTBI and document their recovery trajectories; 2) Evaluate a broad range of novel and established prognostic factors for inclusion in a predictive model for PPCS.

Methods and analysis The Concussion Recovery Study *(CREST)* is a prospective, longitudinal observational cohort study conducted in Perth, Western Australia. *CREST* is recruiting adults aged 18-65 from medical and community-based settings with acute diagnosis of mTBI. *CREST* will create a state-wide research database of mTBI cases, with data being collected in two phases. *Phase I* collates data on demographics, medical background, lifestyle habits, nature of injury and acute mTBI symptomatology. In *Phase II*, participants undergo neuropsychological evaluation, exercise tolerance and vestibular/ocular motor screening, MRI, quantitative electroencephalography, and blood-based biomarker assessment. Follow-up is conducted *via* telephone interview at 1-, 3-, 6- and 12-months after injury. Primary outcome measures are presence of PPCS and Quality of Life, as measured by the Post-Concussion Symptom Scale and the Quality of Life after Brain Injury questionnaires, respectively. Multivariate modelling will examine the prognostic value of promising factors.

Ethics and dissemination Human Research Ethics committees of Royal Perth Hospital (#RGS0000003024), Curtin University (HRE2019-0209), Ramsay Health Care (#2009), and St John of God Health Care (#1628) have approved this study protocol. Findings will be published in peer-reviewed journals and presented at scientific conferences.

Trial registration number ACTRN12619001226190

Strengths and limitations of this study

- *CREST* is a prospective, longitudinal cohort study recruiting adult participants who have experienced mTBI *via* hospital emergency departments and community-based pathways in Perth, Western Australia.
- A primary strength of *CREST* is the establishment of a clinical research dataset of mTBI in Western Australia and documentation of variable recovery trajectories, for which there is currently limited data.
- Another asset of *CREST* is the investigation of novel and established pre-injury predictive factors, blood-based biomarkers, neuropsychological tests, exercise tolerance, vestibular/ocular function, and advanced neuroimaging outcome measures with the aim of generating a predictive model from this 'suite' of factors that may be useful for identifying individuals at risk of experiencing delayed recovery following mTBI.
- A primary limitation of this study may be loss to follow-up and resulting missing data points.
- Other limitations include possible selection bias on the basis of geographic location or injury severity, and sample-size constraints pertaining to predictive modelling.

Introduction

Mild traumatic brain injury (mTBI), also known as concussion, accounts for approximately 80% of all traumatic brain injuries occurring both in Australia and worldwide [1]. mTBI is characterised by a rapid, transient change in neurological function [2,3] accompanied by numerous signs and symptoms, the most frequent of which are headache, neck pain, dizziness, difficulty concentrating, and alterations in mood and sleep [4]. mTBI sequelae can be broadly classified into physical, cognitive, emotional and sleep-related domains [5], although the clinical presentation of mTBI is known to vary considerably between individuals [6], significantly hampering development of reliable prognostic tools.

The prevailing notion of mTBI recovery trajectory implies that symptomatic resolution can be expected within approximately two weeks of injury [7–10]. However, it is increasingly realised that recovery is complex and multifactorial [11], and this recovery trajectory which has been previously defined in the literature pertaining to young sportspeople may not necessarily reflect recovery across age, sex, and socioeconomic status. It frequently is cited that 10-20% of individuals who sustain a mTBI will experience symptoms at least 1 month following injury [12], known as persistent post-concussion symptoms (PPCS)[13]. Determining the true prevalence of PPCS has been complicated by the lack of consistent follow-up across studies and the non-specific nature of the condition [14]. The multitudes of documented ramifications stemming from PPCS have contributed to its status as an emergent public health issue. PPCS may profoundly impact an individual's ability to carry out activities of daily living, and can result in functional consequences including delayed or reduced ability to return to work [15,16],

study [17] and playing sport [18], as well as impaired satisfaction and quality of life [19–22]. Furthermore, PPCS has been linked with heightened use of healthcare services [23–25], making it an under-recognised economic burden.

It is not currently possible to identify which individuals will experience delayed recovery at the time of mTBI diagnosis, nor is there a consensus on how to manage patients who experience such a debilitating constellation of symptoms. The ability to predict who will develop PPCS would be of great benefit. From a clinical perspective, a prognostic model would assist with decision-making and management of patient expectations about their recovery. Importantly, it would enable the provision of personalised healthcare to patients by facilitating triage to the most appropriate forms of treatment according to individual needs *before* symptoms become chronic, thereby potentially resulting in improved patient outcomes. Researchers would also benefit from prognostic models, which could be utilised to enrich clinical trials for evidence-based treatments, which aim to prevent or ameliorate the effects of PPCS or other late-stage conditions associated with mTBI, such as Chronic Traumatic Encephalopathy [26–31] or Alzheimer's disease [32–34].

A plethora of studies have been conducted assessing biomarkers and other factors for their capacity to predict outcome following mTBI. However, variations in study methodologies have resulted in inconsistent results reported in the literature [35,36], and many of the studies conducted to date have been limited to investigating only one type or at best a small subset of prognostic factors [37]. Demographics and injury-related characteristics are amongst the most frequently examined variables, partly because of the convenience with which they can be extracted from medical records. Factors including female sex [38–41], previous history of mTBI [42,43], and pre-injury mental health issues [41,43–48] have all been flagged as potential predictors of PPCS, while others such as age [49], educational status [40,42,50], loss of consciousness [35,48,50,51] and (post-traumatic) amnesia [35,42,52–54] are contentious and require further and more thorough investigation. Reports of poor cognitive function following mTBI has led to the investigation of individual performance on neuropsychological tests as a potential predictor of PPCS. A heightened risk of PPCS has been found amongst individuals who perform poorly on post-mTBI tests of executive function [54], memory [38,55–57] and psychomotor function [53], however, the overall fidelity with which neuropsychological measures alone can prognosticate PPCS has been called into question given that individual performance can be influenced by extraneous factors such as age, prior education, and socio-economic status [58–61]. Consequently, efforts have turned towards identifying and examining other markers of PPCS. Blood-based biomarkers are one viable option that has been embraced by the research community, as they can be a relatively inexpensive and rapid way of assessing the physiological mechanisms that underpin conditions of interest. To date, a vast array of candidate biomarkers pertaining to cellular structural or functional damage as well as the biochemical and molecular

secondary injury cascades have been investigated for their ability to predict outcome after traumatic brain injury [62–64]. While biomarkers such as S100B [65] and the combination of glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) [66] have been proposed to assist with clinical decision making processes relating to traumatic brain injury, studies specifically assessing the relationship between fluid biomarkers and clinical outcome following mTBI have generally yielded small or variable effects [67]. More recently, a host of neuroimaging techniques (e.g. MRI [68], CT [69], PET [70]) and physiological biomarkers (e.g. exercise tolerance [71], vestibular/ocular function [72], psychomotor responses [73]) have also been identified as having the potential to serve as objective markers of PPCS, however, investigations into their prognostic capabilities have yielded inconsistent results and/or been relatively limited, and thus their utility remains to be ascertained. Similarly, the potential for personal predispositions (e.g. resilience [74], coping style [75]) to influence outcome following injury has also been acknowledged, but more research is needed to elucidate the extent of involvement.

Considering that a single predictive variable is unlikely to be the 'silver bullet' that predicts outcome at the level of the individual [35], it is not altogether surprising that research is yet to accurately identify which individuals will experience PPCS. It is increasingly recognised that a more fruitful approach would draw from multiple assessment elements for multivariate prognostic modelling to better calibrate the risk of poor clinical outcomes [35]. No study to date has successfully developed a prediction model that is targeted specifically for prediction of individual patient outcomes following mTBI [35,76]. Efforts to develop validated and pragmatic tools for use in a clinical and/or research context have been impeded by considerable variation between studies and use of suboptimal methodologies across studies [12,76]. Common limitations identified include small and/or selected sample sizes (often resulting from the use of a single centre), recruitment of participants beyond the acute injury period or across a wide post-injury timespan, inconsistencies in definition and measurement of PPCS as well as variable follow-up time points [35,76,77]. Furthermore, prognostic models arising from retrospective study cohorts often encounter additional issues including poor data quality, missing data, minimal use of validated symptom scoring scales, and lack of standardised acute evaluations [77].

The Concussion Recovery Study *(CREST)* is a large, cross-institutional study conducted in Perth, Western Australia (WA), developed with the aim of identifying individuals that are at an increased risk of developing PPCS. Approximately 2.4 million people reside in WA, of which 79% live within the capital city of Perth [78]; the most isolated capital city in the world. The greater Perth area extends a distance of over 125km, occupies an area of 6418 km^2 [79], and is served by 10 Emergency Departments (EDs: 1 private and 9 public, of which 1 is maternity and 1 is child/adolescent exclusively). *CREST* is collecting longitudinal data in two phases and utilises a multivariate, 'suite-based' approach that incorporates demographics, injury-related characteristics, neuropsychological assessment, blood-based

biomarkers, MRI, qEEG, exercise tolerance and vestibular/ocular function to develop an evidence-based acute predictive model for PPCS. The study hypothesises that a suite of pre-injury factors and outcome measures that are assessed during the early presentation period may be used to predict those at risk of experiencing PPCS compared to those who recover within a typical timeframe. It is predicted that a combination of these outcome measures will provide superior discriminatory capacity relative to any single marker used in isolation.

Objectives

The primary objectives of *CREST* are:

1. To establish a large-scale clinical research dataset of adults experiencing mTBI in Western Australia, in order to observe the typical pattern of recovery from mTBI and determine the incidence of PPCS within the Western Australian context.

2. To identify a suite of pre-injury factors and outcome measures during the early presentation period that may be used to predict those at risk of experiencing PPCS compared to those who recover within a typical timeframe.

The secondary objective of the *CREST* study is to:

1. Determine the feasibility of recruiting a large cohort of participants with mTBI from a variety of sources (e.g., EDs, general practitioners (GPs), and community sporting groups), as this widespread collection of community mTBI data has not previously been conducted to this scale in Australia to date.

Methods and Analysis

Patient and Public Involvement A *Community Conversation* was held in August 2018 involving clinicians and general community members with and without a history of mTBI. The conversation took form of a thematic exploration of current management considerations for mTBI, assessment measures, long-term prognosis and symptomatology and contributing factors to recovery. This public consultation highlighted the need for research to determine the predictors for poor outcomes following mTBI and growing interest in combining screening tools, radiological scans, and biological markers for predictive purposes. This stakeholder group shaped the design of the study by highlighting the importance of recruiting participants from the wider community, in addition to clinical populations. The clinicians shaped the *CREST* study's multimodal research design. Several individuals who participated in the *Community Conversation* assisted with recruitment strategies and dissemination of information, although there were not asked to assess the burden of the time required to participate in the research.

Interested members of the group will be consulted at the conclusion of the study to guide dissemination of findings.

Phase I
Inclusion Criteria
• Aged 18-65 years • mTBI within 7 days • Diagnosed with mTBI by medical practitioner
Exclusion Criteria
• Significant history of pre-existing conditions that would interfere with outcome assessment and follow-up (e.g. substance abuse/alcohol abuse, homelessness, terminal illness) • Significant debilitating pre-existing diagnosed mental health disorder that would interfere with neuropsychological and possibly blood biomarker outcome measures, or ability to contact for follow-up (e.g. schizophrenia, bipolar disorder). • Significant pre-existing neurological condition, which may interfere with ability to complete outcome measures or follow-up (e.g. stroke, dementia) • Pre-existing cognitive impairment (e.g. intellectual disability), which may interfere with ability to undertake neuropsychological examination • Non-English speakers or individuals with poor English language skills • Prisoners in custody or people known to be involved in illegal activity • Head injury deemed to be entirely due to primary seizure • Pregnancy
Phase II
Inclusion Criteria
In addition to Phase I Inclusion Criteria • Willing and able to attend the Curtin University and Perron Institute for Neurological and Translational Sciences research tenancies located at the Ralph and Patricia Sarich Neuroscience Research Institute within 7 days of date of injury, and Sir Charles Gardiner Hospital for MRI within 9 days of injury.
Exclusion Criteria
In addition to Phase I Inclusion Criteria 1. Significant other physical trauma that would interfere with physical and/or biochemical outcome assessments and follow-up (e.g. lower limb injuries that would compromise balance or exercise bike testing, or cause changes in blood biomarkers) 2. Any pre-existing heart conditions or other medical conditions that may compromise ability to complete an exercise tolerance test 3. Epilepsy or history of seizure 4. Meets exclusion criteria to undertake MRI, which can be any of the following: a. Has cardiac pacemaker or pacing wire in situ

Study Population & Recruitment Criteria

CREST aims to capture a broad cross-section of community mTBI resulting from a variety of different injury mechanisms (e.g. assault, falls, sports, transport accidents, workplace incidents). Enrolment into *CREST* is open to individuals aged 18 to 65 years who have sustained a medically diagnosed mTBI within the last 7 days. Table 1 details additional inclusion and exclusion criteria for *Phase I* and *Phase II* of the study. Eligibility criterion for referral to the study are straight-forward in design given that in addition to traditional medical-based pathways, the study aims to recruit participants from the general community, who may have a varied understanding of mTBI. We aim to enrol n = 500 participants in *Phase I* of the study.

	b. Has metal surgical clips or staples of any kind (particularly aneurysm clips) in situ c. Has lap band surgery d. Has electronic inner ear implants (bionic ears) e. Has metal fragments in eyes (past or present) f. Has electronic stimulators g. Has implanted pumps h. Has metal pins or rods in bones i. Has an IUCD fitted j. Has shrapnel, bullets or foreign bodies k. Is pregnant l. Has braces m. Has embolization coils* n. Unable to lie flat*

Table 1. Inclusion and Exclusion criteria for *Phase I* and *Phase II* of *CREST*

*Note: *: item not strictly listed as an exclusion criterion but screened for as part of routine practice at the SCGH MRI Department.*

Participant Recruitment Pathways

Recruitment occurs across multiple pathways including major WA Health hospital EDs located throughout the Perth metropolitan area (see Figure 1), GPs, sports physicians, allied health professionals, community/amateur and semi-professional sporting clubs, as well as self-referral to the study. Participants sign a *Participant Referral Form* (PRF; see Supplementary Document 1) consenting for their contact details to be released to the study research team at the medical practitioner's premises (e.g. hospital emergency department or GP), as further described below. Participants are emailed or provided with a written copy of their verbal consent and the participant information sheet at the conclusion of the enrolment interview. Furthermore, *Phase II* participants also receive written documentation of informed consent when they attend the Research Hub, prior to undertaking any of the testing components.

Hospital ED Pathway

Staff at hospital EDs screen for individuals presenting with mTBI for eligibility. Individuals may be considered for *CREST* if they provide a description of an incident likely to have resulted in a mTBI, with accompanying symptoms that can be attributed to that injury as defined by the *World Health Organisation* [80]. Prospective participants must also describe at least one of the following, as described by the *American Congress of Rehabilitation Medicine* [3] and Theadom and colleagues [81].

1. Alteration in mental state at the time of the incident. If present, loss of consciousness must not exceed 30 minutes in duration.
2. Neurological symptoms (e.g. headache, dizziness, fogginess) that may or may not be transient.
3. Memory loss for events immediately before or after the accident. If present, the duration of Post-Traumatic Amnesia must be less than 24 hours.
4. No significant findings on acute brain CT scan, or CT scan not required/performed.

Following the identification of individuals that meet the above criteria, clinicians or research staff assist prospective participants to fill out the PRF -which contains the individuals' date of birth, date of injury and contact details. The PRF functions as a *permission-to-contact* form that permits the hospital to release the participants' contact details to the *CREST* research team. Completed PRFs are emailed or faxed through to a dedicated email address, and *CREST* research team members then use a dedicated mobile telephone number to contact participants within 7 days following the date of injury noted on the PRF.

Community Pathways

In addition to recruiting individuals from Hospital EDs, *CREST* is also recruiting from the general community. The community-based pathway can be broadly categorised into the following three

recruitment streams: *i) General Practitioner (GP)/sports physicians and allied health professionals*, *ii) Community Sports Groups* and *iii) Self-Referral*. Recruitment of prospective participants *via* the community pathways largely mirrors that of the hospital ED pathway.

GPs, sports physicians and allied health professionals

Private GP practices, sports physicians and allied health professionals within the Perth metropolitan area have been informed about the *CREST* study, either by direct in-person approach or by digital communication (e.g. advertisement in professional association newsletters/mailing lists, social media). In this pathway, medical practitioners screen for individuals meeting the above criteria presenting at their practices. Details of interested participants are forwarded *via* email or fax to the *CREST* Research Team using the PRF.

Community Sports Groups

Physiotherapists, athletic trainers and medics at sports clubs approached by the *CREST* research team screen for prospective participants using the aforementioned criteria. If a player experiences a suspected mTBI at training or game day, they are informed of the *CREST* study by the attending first aid personnel, who provide the prospective participant with a copy of the PRF and direct them to seek medical confirmation of mTBI. Should they receive a diagnosis of concussion and wish to participate in the study, individuals can self-refer to the study by contacting the *CREST* Research Team themselves *via* telephone, email or website (https://concussionstudy.com.au/), or by requesting their attending medical professional to forward the PRF to the *CREST* research team on their behalf.

Self-Referral

Individuals from the general community who have sustained an mTBI may participate in the study *via* self-referral, and can do so by directly contacting the *CREST* Research Team *via* telephone, email, fax or website. Individuals recruited using this pathway are asked to provide the name of the medical professional who diagnosed them with an mTBI. In the event that prospective participants have not yet sought medical attention by the time they make contact with the research team, individuals are requested to first seek medical confirmation of mTBI. If prospective participants are able to meet this request and make contact with the research team within 7 days of date of injury, they remain eligible for study enrolment.

Study Design

CREST is a prospective, longitudinal observational cohort study, which follows participants over the course of one year after their mTBI. Individuals who do not develop PPCS serve as controls, which is in line with the study's second primary objective of identifying factors that may be able to discriminate between individuals who do and do not follow a typical recovery trajectory following mTBI. The study

comprises of two parts, referred to as *'Phase I'* and *'Phase II'*, respectively, and follow-ups conducted at multiple time points. This study design was primarily adopted to maximise recruitment efforts. Very little research has been conducted in WA with respect to mTBI, and this two-part approach will help foster greater inclusivity and representation by allowing individuals to partake in the research despite the tyranny of distance. This is particularly pertinent to individuals residing in rural and regional areas of Western Australia, whom can be underrepresented in research studies. The inclusion of this demographic may also provide insights into otherwise unknown factors that may influence recovery following mTBI. Figure 2 provides a graphical depiction of study design. To assess the influence of potential biases, a minimal screening log records basic demographic characteristics of individuals who are referred to the study but do not meet eligibility criteria or decline participation. Furthermore, data being collected as part of *Phase I* will elucidate any differences in the characteristics of individuals who do and do not opt to participate in *Phase II*.

Phase I

Phase I comprises a telephone interview, which is conducted within 7 days of date of injury. This time frame was selected as it encompasses the acute to subacute period following injury, and is prior to anticipated resolution of symptoms in those who experience typical recovery. During this telephone call, information pertaining to demographics, injury-related characteristics, acute post-mTBI clinical care, and medical background, exercise habits and experience of mTBI symptomatology is collected. *Phase I* typically takes 30 minutes to complete. This includes time required to explain the aims and procedures of the study and acquire verbal consent over the telephone, all of which take place prior to collection of data from the participant. Further detail about the data acquired in *Phase I* can be found in Table 2 below.

Phase II

Phase II has been designed to serve as a comprehensive in-person battery of tests, which is also completed within 7 days of date of injury for the reasons stated above. Testing takes place at the Curtin University and Perron Institute for Neurological and Translational Science tenancies, which are both located on the Queen Elizabeth II Medical Centre (QEIIMC) campus in Nedlands (Perth, Western Australia). During this session, qEEG is performed, a blood sample is taken, and neuropsychological, exercise tolerance and vestibular/ocular function testing is conducted. *Phase II* testing typically takes 2.5-3 hours to complete.

MRI is also performed as part of *Phase II* testing. This takes place at the Department of Radiology at Sir Charles Gardiner Hospital located on the QEIIMC campus. Due to the scheduling requirements of

the scanner that is being utilised for the purposes of the study, the MRI is often performed separately to the other *Phase II* components, generally taking place afterhours or on weekends. To accommodate for scanner availability, *CREST* participants may be scanned up to 9 days following the date that they sustained their mTBI.

Follow-Up

Regardless of whether participants opt to complete *Phase I* only, or both *Phase I* and *Phase II*, they are followed-up by telephone interview at 1, 3, 6 and 12 months post-injury. To ensure consistency with follow-up timeframes, the following variations are being adhered to:

- 1 month follow-up is completed at 30 days +/- 4 days from date of injury
- 3 month follow-up is completed at 90 days +/- 7 days from date of injury
- 6 month follow-up is completed at 180 days +/- 14 days from date of injury
- 12 month follow-up is completed at 360 days +/- 30 days from date of injury

The purpose of the follow-up telephone interviews is to document each participant's recovery experience following their mTBI. Thus, at each follow-up time point, information is collected about a number of functional outcomes that may also be predicted. More specifically, these include the individual's return to physical activity, sport, work, and study (if applicable). During the follow-up telephone interviews, participants are also queried about whether or not they have *i)* received or are currently seeking any ongoing allied health, alternative or medical treatments for their mTBI (e.g. physiotherapy, psychotherapy, chiropractic or other medical treatment), *ii)* been diagnosed with a migraine disorder subsequent to the mTBI, and *iii)* sustained another mTBI since the injury that they were enrolled in the study for. Furthermore, the participant's experience of ongoing mTBI symptomatology is ascertained using the *Post Concussion Symptom Scale-22 Item version (PCSS)* [82,83] at each follow-up time point, whilst quality of life is being measured using the short form of the *Quality of Life after Brain Injury* (QOLIBRI-OS:[84]) at the 3-, 6-, and 12-month follow-ups.

Study Completion

Individual participation in the study is considered to be complete at the 12-month follow-up. At no point is a participant considered to be discontinued (i.e. the study participants are not required to complete all of the follow-up interviews). Research team members attempt to contact participants at each of the four individual follow-up time points, regardless of whether or not data was collected for the preceding follow-up time point. A participant is considered to be *'lost to follow-up'* when contact cannot be made with a participant within the follow-up variations stated above, but only for the individual time point in question. Inability to contact participants at follow-up does not preclude participants from participating

in any subsequent follow-ups. Unsuccessful attempts to contact participants are recorded by research team members in a study log. In the event that a participant contacts the research team on their own accord outside of the corresponding follow-up time point variations, such as that which may occur when a participant is responding to a research team member's unsuccessful attempt to contact them *via* telephone or email, data is collected for that time point in the interest of maintaining rapport with the participant; however, this protocol deviation is noted by research team in the participants REDCap® profile and the data collected will not be included in any data analyses.

Data collection: *Phase I*

In *Phase I*, a semi-structured interview is conducted *via* telephone to collect data on participant demographics, circumstances of injury, acute post-mTBI clinical care, medical background, exercise habits and experience of acute mTBI symptomatology. This information is collected using a combination of custom-designed metrics and validated instruments (see Table 2).

Table 2. *Phase I* semi-structured telephone interview/questionnaire components

***Phase I* Telephone Interview/ Questionnaire Components**	
Demographics	Age, sex, height, weight, contact details, next of kin, nominated GP, highest level of completed education
Circumstances of Injury	Description of mechanisms of injury (e.g. sport, non-sport), whether other injuries were sustained during the incident resulting in the mTBI, compensation/litigation status, site/s of impact, loss of consciousness (presence/absence, duration), amnesia (presence/absence, nature: anterograde and retrograde, duration), experience neck pain, presence of seizures or fits following the mTBI, estimated amount of alcohol consumed prior to incident (in standard drinks)
Acute post-mTBI Clinical Care	Details of where medical attention was sought (i.e. ED, GP, First Aid personnel), CT scan performed or not.
Medical Background	Number of previous concussions, including the date and duration of recovery for the most recent concussion, previous whiplash injury (how many in total, date of most recent); whether participants have ever been diagnosed with epilepsy, seizure disorder, migraine or other headache disorder, mental health disorder, sleep disorder, learning disorder: for each of these health conditions, participants are also asked whether they are currently receiving treatment for this disorder (namely, medication and dosage), whether they take prescribed medication on a regular basis (i.e. anti-inflammatory, blood thinners, pain medication, other)
Exercise Habits	Exercise on a regular basis (number of times per week, type of exercise: strength training, cardiovascular exercise, sport)
Acute mTBI symptomatology	*PCSS*

Data Collection: *Phase II*

qEEG

EEG data acquisition and analysis EEG acquisition is conducted using a 19-channel Electro-cap (Electro-Cap International Inc., Eaton, Ohio: USA) and a Mitsar amplifier (Mitsar, Ltd., St Petersburg, Russia), with quantitative and low resolution electromagnetic tomography analysis (LORETA) conducted using NeuroGuide software (Applied Neuroscience, Inc., Florida, USA), which has been extensively validated in the literature, including within populations with mTBI [85,86]. For scalp EEG recording, the participant's head circumference is measured and fitted with an appropriately sized Electro-cap, with all electrodes connected using the standard 10-20 system (See Supplementary Figure 1). Each scalp electrode is prepared by parting the hair and filling it with electroconductive gel (Electro-Gel™, Electro-Cap International Inc, Eaton, Ohio: USA). EEG activity is recorded from 19 scalp electrodes and impedance kept below 10 kΩ, using a linked ears montage, where the ear lobes act as a reference. Resting state data is recorded for 10 minutes, with five-minute eyes open and eyes closed condition blocks. Approximately 60 seconds of artefact-free data will be selected using NeuroGuide software (Applied Neuroscience, Inc.), and individual's activity will be compared to the software's normative database (N = 727). This comparison will provide a Traumatic Brain Injury Index score using a TBI Discriminant Index [86], indicating the severity of the person's TBI ranging from zero to ten (normal = 0, mild = 1 to <3, moderate = 3-5, severe = >5). LORETA analysis and NeuroNavigator software (Applied Neuroscience, Inc., Largo, Florida: USA) will be used to identify areas of dysfunction within networks of interest.

Blood-Based Biomarkers

Blood sample collection and analysis Trained research assistants obtain a 20mL blood sample from non-fasting participants by venepuncture. Whole blood is collected into BD Vacutainer® ethylenediaminetetraacetic acid (EDTA) and serum (SST) blood collection tubes, and rested at room temperature for approximately 30 minutes before centrifugation at 3000 rpm for 10 minutes at 4°C. Samples are then aliquoted into 250 μL vials and put into long-term storage at -80°C until analysis. Blood samples will be analysed by a variety of methods with the intent of quantifying novel and established fluid biomarkers that are associated with mTBI pathophysiology. In particular, protein biomarkers pertaining to neuronal and glial structure and function (e.g. GFAP, UCH-L1), microRNAs, genetic signatures, phenomics and metabolomics will be investigated. An additional whole blood sample is examined using a haematology panel (Mindray BC-2800 Vet Auto Hematology Analyzer; Shenzhen, China) to investigate differences in blood components.

Neuropsychological Assessment and Questionnaires

Participants undergo a brief neuropsychological assessment, which is conducted by trained research team members who have a postgraduate qualification in psychology, under the supervision of a clinical neuropsychologist (CP). The ability to assess a broad range of cognitive domains and executive functions known to be affected by mTBI in a timely manner was the primary driver for the selection of tests comprising the neuropsychological testing battery. More specifically, the *Repeated Battery for the Assessment of Neuropsychological Status Update (RBANS® Update)*[87] is being used to measure immediate and delayed memory, visuospatial constructional skills, language and attention, while the *Trail Making Test Forms A* and *B* [88] are being used to measure components of executive function. Effort is also measured using the *Rey Memory Test* [89]. In addition, participants complete a battery of questionnaires to assess mTBI symptomatology (*PCSS)*: [82,83]), psychological distress (*Depression Anxiety and Stress Scales-21 item version*: [90], and *Brief Symptoms Inventory-18 item version* [91]), resilience (*Brief Resilience Scale*: [92]) and coping style (*Utrecht Coping List*: [93,94]). The neuropsychological assessment and questionnaires are both completed in a private room, and in accordance with standard neuropsychological testing arrangements, with administration time typically taking 30-40 minutes.

Buffalo Concussion Bike Test

Participants undergo exercise tolerance testing using the *Buffalo Concussion Bike Test (BCBT)* as outlined by Haider and colleagues [95] which involves graded exertion on a recumbent bicycle ergometer (Monark RT2, Monark Exercise, Vansbro, Sweden). Prior to conducting the test, participants are screened using the *Physical Activity Readiness Questionnaire (PAR-Q)* [96] to assess for pre-existing cardiac issues or increased risk for cardiopulmonary disease, orthopaedic issues or injuries that may limit their ability to cycle, as well as other medical issues that may impede their ability to complete the exercise test safely. Participants are then asked to rate their current symptoms at rest on a 0 to 10 point visual analogue scale (VAS), and the test is not conducted if their score is 5/10 or more at rest. Heart rate (HR) at rest is determined after five minutes of quiet sitting using a Polar OH1+ armband (Polar Electro Oy, Kempele, Finland). During the test, the participant is asked to maintain a set workload as calculated by a pre-determined formula based upon body weight [95]. Exercise intensity is increased every two minutes by increasing the required workload. HR, rating of perceived exertion (RPE) and symptom exacerbation are also monitored and documented at the end of each stage. RPE is determined using a modified Borg scale, which records an individual's subjective level of exertion on a scale of 6 to 20 [97], and symptom levels on a VAS of 0 to 10 are also recorded. The criteria for ceasing the test include: *i)* symptom exacerbation of more than two points from the pre-exercise value (including an increase in current symptoms or the appearance of a new symptom), *ii)* voluntary exhaustion as ascertained by a RPE exceeding 17, *iii)* judgement by the researcher that the participant

is displaying visible signs of distress, or *iv)* a request by the participant to stop the test. The participant's HR at cessation of the test is recorded as the 'HR threshold'.

Vestibular/Ocular Motor Screening (VOMS) Assessment

The VOMS assessment is a targeted test used to identify vestibular and/or ocular motor dysfunction following mTBI as described by Mucha and colleagues [98]. Briefly, the VOMS involves examining horizontal and vertical smooth pursuits, horizontal and vertical saccades, near point convergence (measured in centimetres), and visual motor sensitivity. Symptoms (namely headache, dizziness, nausea and fogginess) are monitored prior to the commencement of the test, as well as after the completion of each task, to determine the effect of each component on symptom exacerbation. Symptoms are recorded as a score on a VAS ranging from 0 to 10, and the test is ceased if symptoms increase by three points. Any abnormal findings or provocation of symptoms is considered a 'positive' test, and a potential indicator of vestibular/ocular system dysfunction. The *VOMS* takes approximately 5-10 minutes to complete.

Magnetic Resonance Imaging (MRI)

MRI Acquisition MRI is conducted using a Philips Ingenia 3T Multi Transmit Wide Bore Scanner (Philips Healthcare, Best, The Netherlands) equipped with a 32-channel head coil. The imaging protocol takes approximately 50 minutes to compete and comprises standardised sequences as outlined in Table 3.

Table 3. List of *CREST* MRI sequences and their associated purpose

Sequence	**Purpose**
T_1- weighted magnetisation-prepared rapid gradient echo (MPRAGE)	Gray and white matter morphometry Anatomical reference
Susceptibility Weighted Imaging (SWI)	Quantitative Susceptibility Mapping (QSM)
Resting state functional magnetic resonance imaging (rs-fMRI)	Brain connectivity Correlation with qEEG findings
Pseudo-continuous Arterial Spin-Labelling (pcASL)	Cerebral blood flow
Diffusion Weighted Imaging (DWI)	White matter microstructure

MRI Data Analysis Custom-built automated data processing pipelines will be constructed in Python under the Nipype framework [99] on Linux (Ubuntu 18.04 Bionic Beaver distribution) and deployed using Jupyter Notebook [100]. Raw DICOM data are concerted to NIfTI format and stored for analysis according to the Brain Imaging Data Structure (BIDS; [101]) recommendations.

Brain morphometry

T1-weighted data will be processed using Freesurfer image analysis software (http://surfer.nmr.mgh.harvard.edu/), from which volumetric and cortical thickness measurements will be extracted. Data may also be explored using voxel-based morphometry via SPM12 (https://www.fil.ion.ucl.ac.uk/spm/) in MATLAB (The MathWorks, Inc., Natick, Massacheusetts: USA).

Quantitative Susceptibility Mapping

SWI images will be preprocessed for QSM using the MEDI toolbox (http://pre.weill.cornell.edu/mri/pages/qsm.html) in MATLAB. This preprocessing toolbox includes removal of phase inconsistencies, estimation of frequency offset, phase unwrapping, and background field removal using projection onto dipole fields, followed by Morphology enabled dipole inversion (MEDI). Reconstructed QSM images will be explored for iron and calcium concentration using a region of interest (ROI)-based approach.

Resting state functional MRI

Images will be preprocessed using ANTS, FreeSurfer, SPM and aCompCor. Standard preprocessing methods will be employed, including despiking, slice time and motion correction, spatial normalisation to the MNI template, temporal normalisation, linear regression and bandpass filtering. Data will be explored using network connectivity and graph theoretic analysis.

Pseudo-continuous Arterial Spin Labelling

pCASL images will be used to quantify cerebral blood flow (CBF) using the BASIL toolkit in FSL (https://asl-docs.readthedocs.io/en/latest/index.html), with preprocessing including kinetic-model inversion using a Bayesian algorithm, calculation of the magnetization of arterial blood, and registration to MNI space. Data will be probed for both global and ROI-based analyses of CBF.

Diffusion MRI

Diffusion MRI image preprocessing will leverage FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl) and MRtrix software, with a pipeline including skull stripping, Gibbs deranging, correction for motion and eddy currents and susceptibility artefacts and bias field correction. Constrained spherical deconvolution will be used to estimate the white matter fibre Orientation Distribution Function. Outputs will be registered to MNI space for voxel-based exploration of white matter alteration via tract-based spatial statistics (TBSS; [102]) alongside ROI-based analysis for diffusion MRI metrics.

Clinical notification All MRI scans are reported by a neuroradiologist with medically relevant incidental findings communicated to the participant's nominated GP.

General Data Management Plan

CREST's study design requires data collection using various media, including electronic and paper formats. Data acquired electronically (e.g. *Phase I* telephone interview) are being entered directly into a secure, encrypted REDCap® [103,104] database hosted by Curtin University, effectively serving as a standardized case form. Paper copies of participant's personal information (e.g. PRF, results from *Phase II* components) are stored securely in a locked filing cabinet at the research office, and are also digitised and uploaded to REDCap® for storage. Imaging data (i.e. qEEG, MRI) are being organised according to the BIDS and are stored on a secure, cloud-based storage platform also provided by Curtin University, as well as on securely stored physical hard drives for long-term storage.

Upon enrolment into the study, all participants are assigned a unique identification number, and all data that are collected from participants are identified by this number. A master list containing select identifying information is securely stored on an encrypted server, and is available only to authorised research staff. All identifiable information accrued for the purpose of the research study is treated as strictly confidential, and will only be disclosed with permission from participants or as required by law. In line with WA Health guidelines, all research data will be retained for at least seven years.

Data Analysis Plan

PCSS Diagnosis PPCS will be diagnosed using the *Post Concussion Symptoms Scale* (PCSS). This questionnaire is listed as a NINDS-Common Data Element, although there are no definitive rules for implementing a threshold for determining the presence of PPCS. As described in Alla et al., (2012) [105], we will be applying a threshold of 6 or more for males and 7 or more for females on the PCSS. Diagnosis of PPCS will be made at 3 months post-injury, and will be revisited independently at the 6 and 12 months follow-ups.

Statistical Analysis Plan This is the first registry of its kind in WA. There is limited existing data from which to extrapolate power for calculations. Nevertheless, *Phase I* is considered to be appropriately powered to detect known potentially predictive indicators from pre-injury and demographic factors. Our data analysis plan of analysing modalities separately will ensure that *Phase II* is sufficiently powered to detect particularly promising differences. It is acknowledged that only a select number of variables can be included in the multivariate model, and these will be identified using regression

analyses. Only those that are identified to be most promising based on these analyses will be included in the final multivariate model.

Baseline characteristics will be compared using Chi-square tests for categorical variables and t-tests for continuous variables, with respect to outcome (PPCS or no PPCS). In order to identify suitable indicators, each type of outcome measure will be analysed separately, and the most promising measures identified. For example, each MRI modality being investigated will be analysed separately, and statistical analyses will be conducted on outcomes relevant to each modality (e.g. concentrations in regions of interest for particular brain structures in QSM images will be quantified and compared in individuals who are 'diagnosed' with PPCS and those who are deemed to have recovered). Receiver Operating Characteristic (ROC) analysis will be used to determine a discriminate index to separate PPCS from typical recovery. Standard regression modelling will be used to build best-performing prediction models for each of the outcomes of interest, using principal component analysis to identify the most promising predictive indicators to include in the model. The most predictive outcomes for each modality will be identified and can be used in multivariate modelling combining the most promising outcomes from the multiple modalities. Multiple measures of model performance, including calibration and discrimination as well as novel measures employing reclassification tables and net reclassification improvement will be used to establish the best and most parsimonious prediction model. This could help define criteria for further validation studies in future.

Missing data will be handled on a case-by-case basis and appropriate approaches will be implemented under the guidance of a biostatistician. The study purpose is to identify predictors of PPCs at various time points post-injury. An advantage of such an approach is that if certain follow-up time points are missed, analysis can still proceed.

Ethics and Dissemination

Ethics approval for the study has been directly obtained from the Human Research Ethics Committees (HRECs) at all of the institutions involved in the study, or where applicable, reciprocal approval has been granted. Informed verbal consent is obtained from all participants over the telephone as part of enrolment into the study, before data is collected in *Phase I*. Participants are provided with a copy of their verbal consent and study information documentation *via* email following the *Phase I* interview. Written consent is also sought from those participants partaking in *Phase II* prior to the undertaking of any testing components. All data and samples are managed entirely anonymously with the exception of the required information for follow-up telephone calls. There are few significant risks to the participants in this study, and for those that have been identified, appropriate protocols have been devised which have been approved by the HRECs. Participants can withdraw from the study at any time and this will not have any impact on their clinical care. Data contributed to the study can also be withdrawn upon request. The results of this study will be published in peer-reviewed journals and presented at local,

domestic and international scientific meetings. No identifiable information will be published, unless permission has been obtained from participants to do so.

Discussion

Relative to studies previously conducted in the field, two main advantages distinguish the *CREST* study by design to provide superior insight into the recovery trajectory of individuals sustaining an mTBI. First: *CREST* is recruiting widely from a number of different clinical and community-based sources, with scope to recruit from regional/rural and remote areas in future. Not only will this facilitate the simultaneous observation of recovery trajectories associated with a variety of different mTBI injury mechanisms, but it will also provide insight into whether some factors may be more salient for recovery following mTBI due to different causal mechanisms. This unique recruitment approach will also provide much needed data regarding the circumstances under which mTBI occurs within WA as well as the incidence and prevalence of both mTBI and PPCS that may ensue, for which data is significantly limited. Second: *CREST* utilises an extensive testing battery that comprises a broad range of both novel and established predictors of PPCS. This in itself is significant for several reasons: First and foremost, such an approach will enable the evaluation of previously identified factors in a novel, community based cohort that has been followed-up over a prolonged period of time. Furthermore, it features several novel techniques (e.g. QSM, qEEG, metabolomics, proteomics) that have received limited attention and others (e.g. exercise tolerance) that have been investigated only in specific populations (e.g. adolescent athletes), expounding the utility of such methods. The systematic approach adopted by *CREST* in which data is being collected also creates a fertile setting for the examination of novel or poorly investigated relationships between different clinical parameters predictive of poor outcome (e.g. congruency between qEEG and rs-fMRI; ASL and exercise tolerance), and provides opportunity for economic evaluation of diagnostic and prognostic methods from both the healthcare and consumer perspectives. Taken together, this research has the potential to empower clinicians and researchers alike by identifying factors that may contribute to the development of an optimal 'suite' of rapidly deployable predictive variables for the early identification of PPCS risk. It also has the potential to assist with the early identification of patients at risk of experiencing PPCS and enable timely patient-centred treatment, and thereby help to reduce the personal, economic and societal burden of mTBI.

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Authors' contributions MF DF CP MB ML SR DX conceptualised the study and participated in initial study design, with assistance from AG JT ET FB AvH. AG, SCH, JT, FB and MF drafted the manuscript. AG prepared visual content and coordinated manuscript revisions. MF DF CP MB ML SR DX obtained the research funding. All other authors (ET SM AR GA BS SvS PB JI AC AM DX SR SH GC ML MB CP DF) contributed to study design and revisions of the manuscript.

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Competing Interests Melinda Fitzgerald is the Chief Executive Officer of the charitable organization *Vision TBI (Ltd.)*, trading as *Connectivity - Traumatic Brain Injury Australia*. AG acknowledges the Perron Institute for Neurological and Translational Sciences for PhD stipend support.

Patient consent for publication Not required.

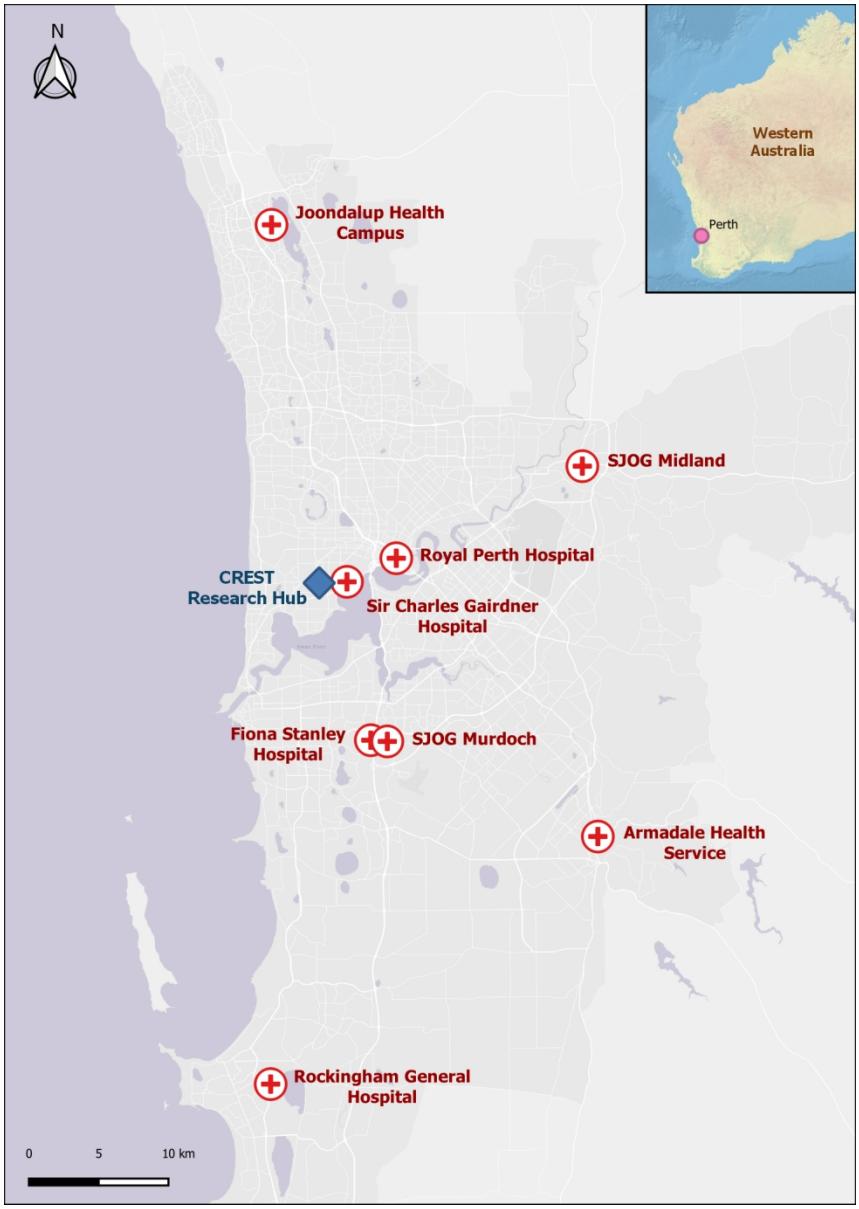
Ethics Approval This study protocol has been approved by the Human Research Ethics committees of Royal Perth Hospital (#RGS0000003024), Curtin University (HRE2019-0209), Ramsay Health Care (#2009), and St John of God Health Care (#1628).

Provenance and peer review Not commissioned; externally peer reviewed

Figure Legends

Figure 1. Map showing location of hospital emergency departments (red crosses) throughout the Greater Perth Area from which prospective *CREST* participants are recruited, relative to the location of the *CREST* Research Hub (blue diamond). *Note:* SJOG: Saint John of God Hospital

Figure 2. Flow diagram of the *CREST* study design. Participants are recruited *via* Hospital ED or Community-Based Pathways using a dedicated *Participant Referral Form*. Following the receipt of a completed *Participant Referral Form*, either by email or fax, a member of the *CREST* research team uses a dedicated mobile telephone number to contact prospective participants. During this phone call, interested participants are briefed on the study aims and procedures, and verbal consent is obtained to participate in the study. Following this, the *Phase I* semi-structured telephone interview is conducted and upon its conclusion participants are asked if they also wish to participate in *Phase II* of the study. If interested, the *CREST* research team member completes a telephone screen to assess the participant's eligibility to undertake the additional components of *Phase II*. If a participant is deemed eligible, a testing session is organised at the *CREST* Research Hub. Both *Phase I* and *Phase II* components are conducted within 7 days of a participant sustaining an mTBI. All participants are followed-up by telephone interview at 1-, 3-, 6- and 12-months following the date of injury. *Note:* * Comprises the Curtin University and Perron Institute for Neurological and Translational Science tenancies, which are located at Queen Elizabeth II Medical Centre, Nedlands (Perth, Western Australia); †: MRI may be conducted up to 9 days following participant's mTBI; ‡: Quality of Life is assessed using the QOLIBRI-OS at 3-, 6- and 12-month follow-ups only. Abbreviations: EDs: Emergency departments; GPs: General practitioners; MRI: Magnetic resonance imaging; mTBI: mild traumatic brain injury; NPA: Neuropsychological assessment; qEEG: Quantitative electroencephalography; VOMS: Vestibular/Ocular Motor Screening test; WA: Western Australia.



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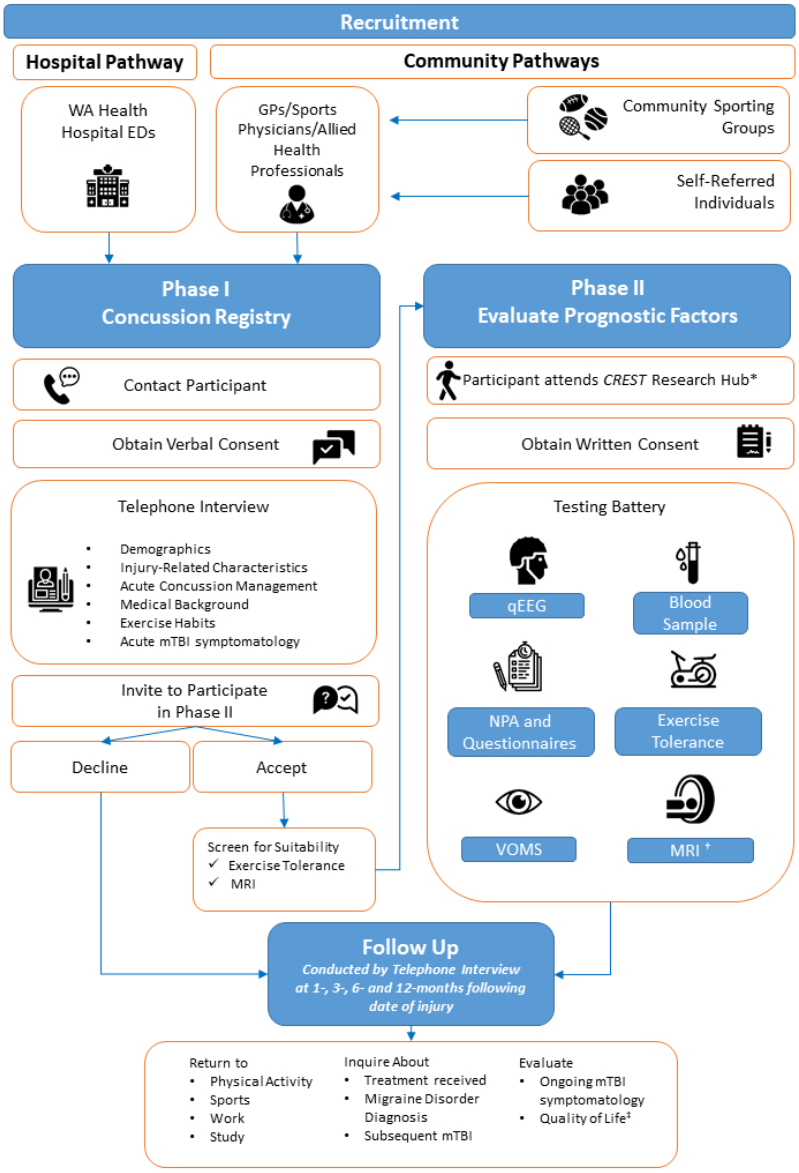

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190x275mm (96 x 96 DPI)

Predicting Outcome Following Mild Traumatic Brain Injury: Protocol for the Longitudinal, Prospective, Observational Concussion Recovery (*CREST)* Cohort Study

Gozt, AK et al.

Supplementary information

1. Document 1. Participant site referral form.
2. Figure 1. The 10-20 International system of EEG electrode placement.
3. Table 1. MRI scan parameters.

CURTIN HEALTH INNOVATION RESEARCH INSTITUTE | Curtin University | perron institute for neurological and translational science

CREST Concussion REcovery STudy

Participant Referral Form

Patient Name: **DOB:** / /

Phone: **Date of Injury:** / /

Email:

I consent to _____ (*Name of Healthcare Provider*) providing my details above to the Concussion Study team and to a member of that team contacting me to discuss the Concussion Study in more detail.

Patient Signature: **Date:**

MEDICAL PRACTITIONER TO COMPLETE THIS SECTION

Referring Doctor or Healthcare Provider Details

Name:

Practice Details or Stamp:

Signature: **Date:** / /

Key Participant Selection Criteria:

Identifying potential participants: To determine if a concussion has occurred, potential participants may be considered for this study if they provide a description of an incident likely to lead to a traumatic brain injury, with accompanying neurological signs and symptoms which can be attributed to that injury, as defined by the World Health Organisation. Participants must also describe **at least one** of the following, as described by the American Congress of Rehabilitation Medicine and Theadom and colleagues:

1. Any period of loss of consciousness (Were you "knocked out")?
2. Alteration in mental state at the time of the accident (Were you dazed, disoriented or confused? Did you "see stars" at the time of injury?)
3. Any memory loss for events immediately before or after the accident (Do you have any memory loss around the time of injury - before or after?)
4. Any neurological deficits (eg headache, dizziness, fogginess) that may or may not be transient?

Please forward the completed form to:

concussionstudy@curtin.edu.au

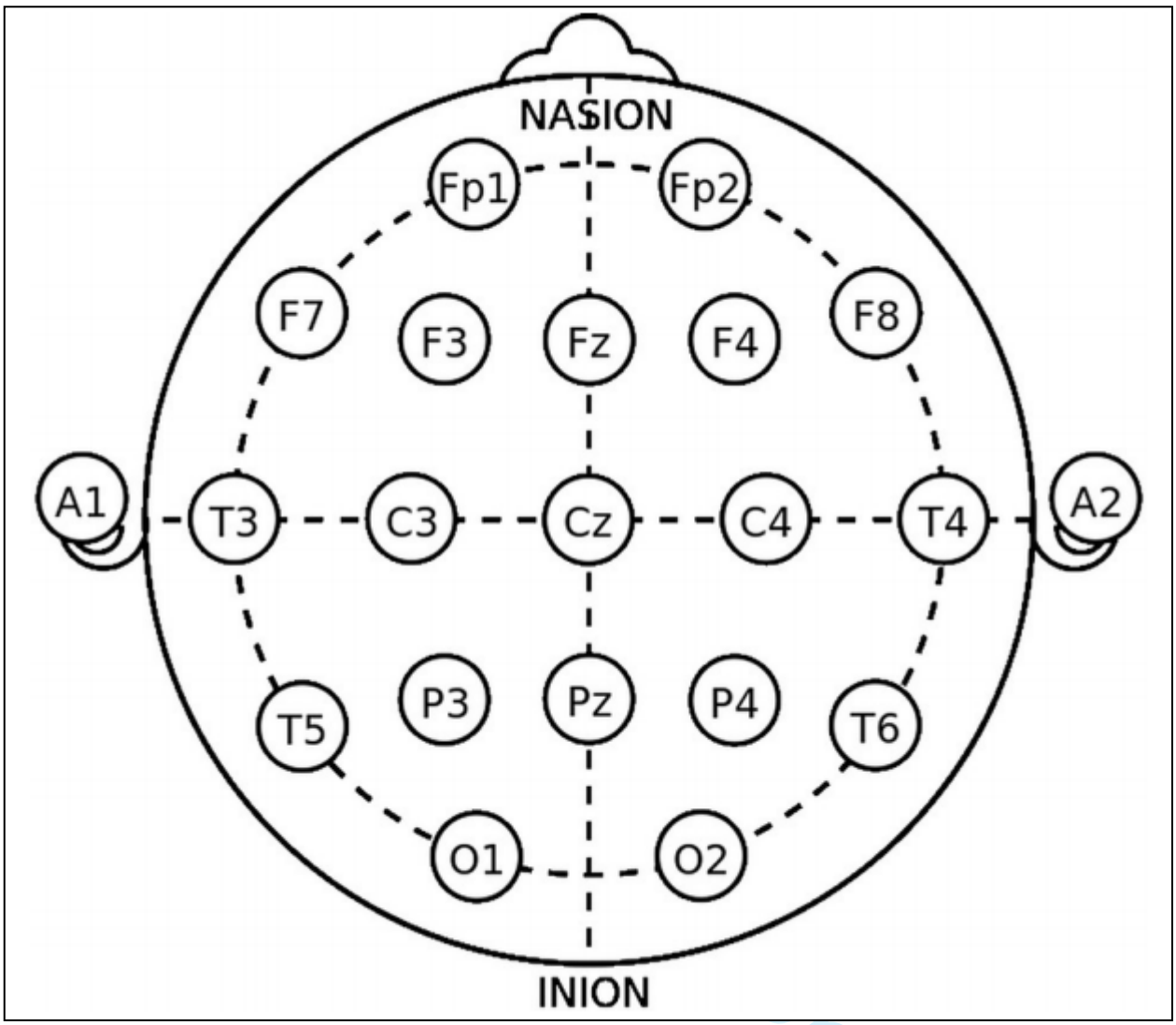
or

Secure e-fax 08 6270 5470

Thank you very much for your participation!

This study has Ethics Approval through Royal Perth Hospital Human Research Ethics Committee (#RGS0000003024) and Curtin University (HRE2019-0209). Please contact the Curtin research team on 0466 526 849 if you have any further questions.

Supplementary Figure 1. The 10-20 International system of EEG electrode placement.



Note: Figure adapted from Rojas G, Alvarez C, Montoya C, et al. Study of resting-state functional connectivity using EEG electrodes position as seed. *Front Neurosci*;12 doi:10.3389/fins.2018.00235 [published Online First 24 April 2018]

Supplementary Table 1. MRI scan parameters.

Sequence	T1	3D FLAIR	3D SWI	rs-fMRI	pCASL	DTI
Orientation	Transverse	Sagittal	Transverse	Transverse	Transverse	Transverse
Voxel size (mm)	1 x 1 x 1	1 x 1 x 1	0.7 x 0.7 x 1.4	3 x 3 x 3	3.75 x 4 x 8	2 x 2 x 2
TR (ms)	6.01	4,800	33.4	3,000	4,064	4,694
TE (ms)	2.7	302	5/4 echoes Δ7.7	30	11.17	113
TI (ms)	-	1600	-	-	-	-
Flip angle (deg)	8	90	10	90	90	90
Phase FOV (mm)	256	182.5	220	216	240	224
Matrix size	256 x 256	252 x 252	301 x 301	69 x 69	88 x 88	110 x 110
# slices	175	365	110	46	15	60
Fat suppression	no	no	no	yes	yes	yes
b-values (sec/mm^2) [directions]	-	-	-	-	-	0, 1500 [32]
Time (min)	6:19	3:31	9:40	7:42 [a]	4:45[b]	11:36

Note: [a]: 150 dynamics; [b]: Post-label delay 1800ms