

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-046460
Article Type:	Protocol
Date Submitted by the Author:	30-Oct-2020
Complete List of Authors:	<p>Gozt, Aleksandra; Curtin University Faculty of Health Sciences, Curtin Health Innovation Research Institute; Perron Institute of Neurological and Translational Science</p> <p>Hellewell, Sarah; Curtin University Faculty of Health Sciences, Curtin Health Innovation Research Institute</p> <p>Thorne, Jacinta; Curtin University Faculty of Health Sciences, Curtin Health Innovation Research Institute</p> <p>Thomas, Elizabeth; Curtin University, Centre for Clinical Research Excellence, School of Public Health; The University of Western Australia, Division of Surgery, Faculty of Health & Medical Sciences</p> <p>Buhagiar, Francesca; The University of Western Australia Faculty of Science, School of Psychological Science</p> <p>Markovic, Shaun; Murdoch University, Discipline of Exercise Science; Australian Alzheimer's Research Foundation</p> <p>Van Houselt, Anoek; The University of Western Australia Faculty of Science, School of Human Sciences</p> <p>Ring, Alexander; Murdoch University, Institute for Immunology and Infectious Diseases; Curtin University Faculty of Health Sciences, School of Physiotherapy and Exercise Science</p> <p>Arendts, Glenn; Fiona Stanley Hospital, Emergency Department; Harry Perkins Institute of Medical Research, Centre for Clinical Research in Emergency Medicine</p> <p>Smedley, Benjamin; Rockingham General Hospital, Emergency Department</p> <p>Van Schalkwyk, Sjinene; Joondalup Health Campus, Emergency Department</p> <p>Brooks, Philip; Saint John of God Midland Public Hospital, Emergency Department; School of Medicine, The University of Notre Dame and Curtin Medical School, Curtin University</p> <p>Illiff, John ; Saint John of God Hospital Murdoch and Royal Perth Hospital, Emergency Departments; Royal Flying Doctor Service of Australia- Western Operations and Curtin Medical School, Curtin University</p> <p>Celenza, Antonio; Sir Charles Gairdner Hospital, Emergency Department; The University of Western Australia, Division of Emergency Medicine, School of Medicine</p> <p>Mukherjee, Ashes; Armadale Health Service, Emergency Department</p> <p>Xu, Dan; Curtin University Bentley Campus, Centre for Clinical Research Excellence, School of Public Health</p>

	<p>Robinson, Suzanne; Curtin University Faculty of Health Sciences, School of Public Health</p> <p>Honeybul, Stephen; Department of Health Government of Western Australia, Statewide Director of Neurosurgery; Sir Charles Gairdner Hospital, Royal Perth Hospital and Fiona Stanley Hospital, Head of Department</p> <p>Cowen, Gill; Curtin University, Curtin Medical School</p> <p>Licari, Melissa; Telethon Kids Institute; The University of Western Australia Faculty of Science, School of Human Sciences</p> <p>Bynevelt, Michael; The University of Western Australia, Division of Surgery, School of Medicine; The Neurological Intervention & Imaging Service of Western Australia at Sir Charles Gairdner Hospital</p> <p>Pestell, Carmela; The University of Western Australia Faculty of Science, School of Psychological Science; Curtin University Faculty of Health Sciences, Curtin Health Innovation Research Institute</p> <p>Fatovich, Daniel; The University of Western Australia, Emergency Medicine, Royal Perth Hospital; Harry Perkins Institute of Medical Research, Centre for Clinical Research in Emergency Medicine</p> <p>Fitzgerald, Melinda; Curtin University Faculty of Health Sciences, Curtin Health Innovation Research Institute; Perron Institute for Neurological and Translational Sciences</p>
Keywords:	<p>Neuroradiology < RADIOLOGY & IMAGING, MENTAL HEALTH, Neurobiology < NATURAL SCIENCE DISCIPLINES, Neurological injury < NEUROLOGY, NEUROLOGY, Neuropathology < PATHOLOGY</p>

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 1 Predicting Outcome Following Mild Traumatic Brain Injury: Protocol for the Longitudinal,
4 2 Prospective, Observational Concussion Recovery (*CREST*) Cohort Study
5 3
6 4
7 5

8 4 Aleksandra Gozt^{1,2}, Sarah C. Hellewell¹, Jacinta Thorne¹, Elizabeth Thomas^{3,4}, Francesca Buhagiar⁵,
9 5 Shaun Markovic^{6,7}, Anoeck van Houselt⁸, Alexander Ring^{9,10}, Glenn Arendts^{11,12},
10 6 Benjamin Smedley¹³, Sjinene van Schalkwyk¹⁴, Philip Brooks^{15,16,17} John Iliff^{17,18,19,20},
11 7 Antonio Celenza^{21,22}, Ashes Mukherjee²³, Dan Xu³, Suzanne Robinson³, Stephen Honeybul^{24,25,26,27},
12 8 Gill Cowen¹⁷, Melissa Licari^{8,28}, Michael Bynevelt^{4,29}, Carmela Pestell^{1,5}, Daniel Fatovich^{12,30},
13 9 Melinda Fitzgerald^{1,2}
14 10
15 11
16 12
17 13
18 14
19 15
20 16
21 17
22 18
23 19
24 20
25 21
26 22
27 23
28 24
29 25
30 26
31 27
32 28
33 29
34 30
35 31
36 32
37 33
38 34
39 35
40 36
41 37
42 38
43 39
44 40
45 41
46 42
47 43
48 44
49 45
50 46
51 47
52 48
53 49
54 50
55 51
56 52
57 53
58 54
59 55
60 56

26 Corresponding Author:

27 Melinda Fitzgerald

28 Curtin University/Perron Institute for Neurological and Translational Science

29 8 Verdun Street, Nedlands, WA 6009, Australia

30 Email: lindy.fitzgerald@curtin.edu.au
31
32

33 Abstract word count: 300 words

34 Word count: 5423 words

35 Figures: 2

36 Tables: 3

37 Supplementary items: 3

1
2
3 **Abstract**

4 **Introduction** Mild traumatic brain injury (mTBI) is a complex injury with heterogeneous physical,
5
6 cognitive, emotional and functional outcomes. Many who sustain mTBI recover within two weeks of
7
8 injury, however, approximately 10-20% of individuals experience mTBI symptoms beyond this 'typical'
9
10 recovery timeframe; known as persistent post-concussion symptoms (PPCS). Despite increasing
11
12 interest in PPCS, uncertainty remains regarding its prevalence in community-based populations and the
13
14 extent to which poor recovery may be identified using early predictive markers.
15

16 **Objective** 1) Establish a research database of people who have experienced mTBI and document their
17
18 recovery trajectories; 2) Evaluate a broad range of novel and established prognostic factors for inclusion
19
20 in a predictive model for PPCS.
21

22 **Methods and analysis** The Concussion Recovery Study (*CREST*) is a prospective, longitudinal
23
24 observational cohort study conducted in Perth, Western Australia. *CREST* is recruiting adults aged 18-
25
26 65 from medical and community-based settings with acute diagnosis of mTBI. *CREST* will create a
27
28 state-wide research database of mTBI cases, with data being collected in two phases. *Phase I* collates
29
30 data on demographics, medical background, lifestyle habits, nature of injury and acute mTBI
31
32 symptomatology. In *Phase II*, participants undergo neuropsychological evaluation, exercise tolerance
33
34 and vestibular/ocular motor screening, MRI, quantitative electroencephalography, and blood-based
35
36 biomarker assessment. Follow-up is conducted *via* telephone interview at 1-, 3-, 6- and 12-months after
37
38 injury. Primary outcome measures are presence of PPCS and Quality of Life, as measured by the Post-
39
40 Concussion Symptom Scale and the Quality of Life after Brain Injury questionnaires, respectively.
41
42 Multivariate modelling will examine the prognostic value of promising factors.
43

44 **Ethics and dissemination** Human Research Ethics committees of Royal Perth Hospital
45
46 (#RGS0000003024), Curtin University (HRE2019-0209), Ramsay Health Care (#2009), and St John of
47
48 God Health Care (#1628) have approved this study protocol. Findings will be published in peer-
49
50 reviewed journals and presented at scientific conferences.
51

52 **Trial registration number** ACTRN12619001226190
53
54
55
56
57
58
59
60

68 **Strengths and limitations of this study**

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

84 **Introduction**

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

92
93 The prevailing notion of mTBI recovery trajectory implies that symptomatic resolution can be expected
94 within approximately two weeks of injury [7–10]. However, it is increasingly realised that recovery is
95 complex and multifactorial [11], and this recovery trajectory which has been previously defined in the
96 literature pertaining to young sportspeople may not necessarily reflect recovery across age, sex, and
97 socioeconomic status. It frequently is cited that 10-20% of individuals who sustain a mTBI will
98 experience symptoms at least 1 month following injury [12], known as persistent post-concussion
99 symptoms (PPCS)[13]. Determining the true prevalence of PPCS has been complicated by the lack of
100 consistent follow-up across studies and the non-specific nature of the condition [14]. The multitudes of
101 documented ramifications stemming from PPCS have contributed to its status as an emergent public
102 health issue. PPCS may profoundly impact an individual’s ability to carry out activities of daily living,
103 and can result in functional consequences including delayed or reduced ability to return to work [15,16],

1
2
3 104 study [17] and playing sport [18], as well as impaired satisfaction and quality of life [19–22].
4
5 105 Furthermore, PPCS has been linked with heightened use of healthcare services [23–25], making it an
6
7 106 under-recognised economic burden.
8
9 107

10 108 It is not currently possible to identify which individuals will experience delayed recovery at the time of
11
12 109 mTBI diagnosis, nor is there a consensus on how to manage patients who experience such a debilitating
13
14 110 constellation of symptoms. The ability to predict who will develop PPCS would be of great benefit.
15
16 111 From a clinical perspective, a prognostic model would assist with decision-making and management of
17
18 112 patient expectations about their recovery. Importantly, it would enable the provision of personalised
19
20 113 healthcare to patients by facilitating triage to the most appropriate forms of treatment according to
21
22 114 individual needs *before* symptoms become chronic, thereby potentially resulting in improved patient
23
24 115 outcomes. Researchers would also benefit from prognostic models, which could be utilised to enrich
25
26 116 clinical trials for evidence-based treatments, which aim to prevent or ameliorate the effects of PPCS or
27
28 117 other late-stage conditions associated with mTBI, such as Chronic Traumatic Encephalopathy [26–31]
29
30 118 or Alzheimer’s disease [32–34].
31
32 119

33 120 A plethora of studies have been conducted assessing biomarkers and other factors for their capacity to
34
35 121 predict outcome following mTBI. However, variations in study methodologies have resulted in
36
37 122 inconsistent results reported in the literature [35,36], and many of the studies conducted to date have
38
39 123 been limited to investigating only one type or at best a small subset of prognostic factors [37].
40
41 124 Demographics and injury-related characteristics are amongst the most frequently examined variables,
42
43 125 partly because of the convenience with which they can be extracted from medical records. Factors
44
45 126 including female sex [38–41], previous history of mTBI [42,43], and pre-injury mental health issues
46
47 127 [41,43–48] have all been flagged as potential predictors of PPCS, while others such as age [49],
48
49 128 educational status [40,42,50], loss of consciousness [35,48,50,51] and (post-traumatic) amnesia
50
51 129 [35,42,52–54] are contentious and require further and more thorough investigation. Reports of poor
52
53 130 cognitive function following mTBI has led to the investigation of individual performance on
54
55 131 neuropsychological tests as a potential predictor of PPCS. A heightened risk of PPCS has been found
56
57 132 amongst individuals who perform poorly on post-mTBI tests of executive function [54], memory
58
59 133 [38,55–57] and psychomotor function [53], however, the overall fidelity with which
60
134 neuropsychological measures alone can prognosticate PPCS has been called into question given that
135 individual performance can be influenced by extraneous factors such as age, prior education, and socio-
136 economic status [58–61]. Consequently, efforts have turned towards identifying and examining other
137 markers of PPCS. Blood-based biomarkers are one viable option that has been embraced by the research
138 community, as they can be a relatively inexpensive and rapid way of assessing the physiological
139 mechanisms that underpin conditions of interest. To date, a vast array of candidate biomarkers
140 pertaining to cellular structural or functional damage as well as the biochemical and molecular

1
2
3 141 secondary injury cascades have been investigated for their ability to predict outcome after traumatic
4 142 brain injury [62–64]. While biomarkers such as S100B [65] and the combination of glial fibrillary acidic
5 143 protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) [66] have been proposed to assist
6 144 with clinical decision making processes relating to traumatic brain injury, studies specifically assessing
7 145 the relationship between fluid biomarkers and clinical outcome following mTBI have generally yielded
8 146 small or variable effects [67]. More recently, a host of neuroimaging techniques (e.g. MRI [68], CT
9 147 [69], PET [70]) and physiological biomarkers (e.g. exercise tolerance [71], vestibular/ocular function
10 148 [72], psychomotor responses [73]) have also been identified as having the potential to serve as objective
11 149 markers of PPCS, however, investigations into their prognostic capabilities have yielded inconsistent
12 150 results and/or been relatively limited, and thus their utility remains to be ascertained. Similarly, the
13 151 potential for personal predispositions (e.g. resilience [74], coping style [75]) to influence outcome
14 152 following injury has also been acknowledged, but more research is needed to elucidate the extent of
15 153 involvement.

16 154
17 155 Considering that a single predictive variable is unlikely to be the ‘silver bullet’ that predicts outcome at
18 156 the level of the individual [35], it is not altogether surprising that research is yet to accurately identify
19 157 which individuals will experience PPCS. It is increasingly recognised that a more fruitful approach
20 158 would draw from multiple assessment elements for multivariate prognostic modelling to better calibrate
21 159 the risk of poor clinical outcomes [35]. No study to date has successfully developed a prediction model
22 160 that is targeted specifically for prediction of individual patient outcomes following mTBI [35,76].
23 161 Efforts to develop validated and pragmatic tools for use in a clinical and/or research context have been
24 162 impeded by considerable variation between studies and use of suboptimal methodologies across studies
25 163 [12,76]. Common limitations identified include small and/or selected sample sizes (often resulting from
26 164 the use of a single centre), recruitment of participants beyond the acute injury period or across a wide
27 165 post-injury timespan, inconsistencies in definition and measurement of PPCS as well as variable follow-
28 166 up time points [35,76,77]. Furthermore, prognostic models arising from retrospective study cohorts
29 167 often encounter additional issues including poor data quality, missing data, minimal use of validated
30 168 symptom scoring scales, and lack of standardised acute evaluations [77].

31 169
32 170 The Concussion Recovery Study (*CREST*) is a large, cross-institutional study conducted in Perth,
33 171 Western Australia (WA), developed with the aim of identifying individuals that are at an increased risk
34 172 of developing PPCS. Approximately 2.4 million people reside in WA, of which 79% live within the
35 173 capital city of Perth [78]; the most isolated capital city in the world. The greater Perth area extends a
36 174 distance of over 125km, occupies an area of 6418 km² [79], and is served by 10 Emergency Departments
37 175 (EDs: 1 private and 9 public, of which 1 is maternity and 1 is child/adolescent exclusively). *CREST* is
38 176 collecting longitudinal data in two phases and utilises a multivariate, ‘suite-based’ approach that
39 177 incorporates demographics, injury-related characteristics, neuropsychological assessment, blood-based

1
2
3 178 biomarkers, MRI, qEEG, exercise tolerance and vestibular/ocular function to develop an evidence-
4 based acute predictive model for PPCS.

5 179
6 180
7

8 181

9 182 **Objectives**

10 183 The primary objectives of *CREST* are:

11 184 1. To establish a large-scale clinical research database of adults experiencing mTBI in Western
12 185 Australia, in order to observe the typical pattern of recovery from mTBI and determine the
13 186 incidence of PPCS.

14 187

15 188 2. To identify a suite of pre-injury factors and outcome measures during the early presentation
16 189 period that may be used to predict those at risk of experiencing PPCS compared to those who
17 190 recover within a typical timeframe.

18 191

19 192 The secondary objective of the *CREST* study is to:

20 193 1. Determine the feasibility of recruiting a large cohort of participants with mTBI from a variety
21 194 of sources (e.g., EDs, general practitioners (GPs), and community sporting groups), as this
22 195 widespread collection of community mTBI data has not previously been conducted to this scale
23 196 in Australia or internationally to date.

24 197

25 198

26 199 **Methods and Analysis**

27 200 **Patient and Public Involvement** A *Community Conversation* was held in August 2018 involving
28 201 clinicians and general community members with and without a history of mTBI. The conversation took
29 202 form of a thematic exploration of current management considerations for mTBI, assessment measures,
30 203 long-term prognosis and symptomatology and contributing factors to recovery. This public consultation
31 204 highlighted the need for research to determine the predictors for poor outcomes following mTBI and
32 205 growing interest in combining screening tools, radiological scans, and biological markers for predictive
33 206 purposes. This stakeholder group shaped the design of the study by highlighting the importance of
34 207 recruiting participants from the wider community, in addition to clinical populations. The clinicians
35 208 shaped the *CREST* study's multimodal research design. Several individuals who participated in the
36 209 *Community Conversation* assisted with recruitment strategies and dissemination of information,
37 210 although there were not asked to assess the burden of the time required to participate in the research.
38 211 Interested members of the group will be consulted at the conclusion of the study to guide dissemination
39 212 of findings.

40 213

41 214 **Study Population & Recruitment Criteria**

1
2
3 215 *CREST* aims to capture a broad cross-section of community mTBI resulting from a variety of different
4 216 injury mechanisms (e.g. assault, falls, sports, transport accidents, workplace incidents). Enrolment into
5 217 *CREST* is open to individuals aged 18 to 65 years who have sustained a medically diagnosed mTBI
6 218 within the last 7 days. Table 1 details additional inclusion and exclusion criteria for *Phase I* and *Phase*
7 219 *II* of the study.
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

<i>Phase I</i>	
Inclusion Criteria	
<ul style="list-style-type: none"> • Aged 18-65 years • mTBI within 7 days • Diagnosed with mTBI by medical practitioner 	
Exclusion Criteria	
<ul style="list-style-type: none"> • 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 	
<i>Phase II</i>	
Inclusion Criteria	
<i>In addition to Phase I Inclusion Criteria</i>	
<ul style="list-style-type: none"> • 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	
<i>In addition to Phase I Inclusion Criteria</i>	
<ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> 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* 	

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

223 **Participant Recruitment Pathways**

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

229 **Hospital ED Pathway**

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

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

241
242 Following the identification of individuals that meet the above criteria, clinicians or research staff assist
243 prospective participants to fill out a *Participant Referral Form* (PRF: see Supplementary Document 1),
244 which contains the individuals' date of birth, date of injury and contact details. The PRF functions as a
245 *permission-to-contact* form that permits the hospital to release the participants' contact details to the
246 *CREST* research team. Completed PRFs are emailed or faxed through to a dedicated email address, and
247 *CREST* research team members then use a dedicated mobile telephone number to contact participants
248 within 7 days following the date of injury noted on the PRF.

250 **Community Pathways**

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

257 **GPs, sports physicians and allied health professionals**

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

1
2
3 260 communication (e.g. advertisement in professional association newsletters/ mailing lists, social media).
4
5 261 In this pathway, medical practitioners screen for individuals meeting the above criteria presenting at
6
7 262 their practices. Details of interested participants are forwarded *via* email or fax to the *CREST* Research
8
9 263 Team using the PRF.
10

264

265 **Community Sports Groups**

12 266 Physiotherapists, athletic trainers and medics at sports clubs approached by the *CREST* research team
13
14 267 screen for prospective participants using the aforementioned criteria. If a player experiences a suspected
15
16 268 mTBI at training or game day, they are informed of the *CREST* study by the attending first aid personnel,
17
18 269 who provide the prospective participant with a copy of the PRF and direct them to seek medical
19
20 270 confirmation of mTBI. Should they receive a diagnosis of concussion and wish to participate in the
21
22 271 study, individuals can self-refer to the study by contacting the *CREST* Research Team themselves *via*
23
24 272 telephone, email or website (<https://concussionstudy.com.au/>), or by requesting their attending medical
25
26 273 professional to forward the PRF to the *CREST* research team on their behalf.
27

274

275 **Self-Referral**

28 276 Individuals from the general community who have sustained an mTBI may participate in the study *via*
29
30 277 self-referral, and can do so by directly contacting the *CREST* Research Team *via* telephone, email, fax
31
32 278 or website. Individuals recruited using this pathway are asked to provide the name of the medical
33
34 279 professional who diagnosed them with an mTBI. In the event that prospective participants have not yet
35
36 280 sought medical attention by the time they make contact with the research team, individuals are requested
37
38 281 to first seek medical confirmation of mTBI. If prospective participants are able to meet this request and
39
40 282 make contact with the research team within 7 days of date of injury, they remain eligible for study
41
42 283 enrolment.
43

284

285 **Study Design**

44 286 *CREST* is a prospective, longitudinal observational cohort study, which follows participants over the
45
46 287 course of one year after their mTBI. Individuals who do not develop PPCS serve as controls, which is
47
48 288 in line with the study's second primary objective of identifying factors that may be able to discriminate
49
50 289 between individuals who do and do not follow a typical recovery trajectory following mTBI. The study
51
52 290 comprises of two parts, referred to as '*Phase I*' and '*Phase II*', respectively, and follow-ups conducted
53
54 291 at multiple time points. See Figure 2 for graphical depiction of study design.
55

292

293

294 **Phase I**

58 295 *Phase I* comprises a telephone interview, which is conducted within 7 days of date of injury. During
59
60 296 this telephone call, information pertaining to demographics, injury-related characteristics, acute post-

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

303 ***Phase II***

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

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

318 **Follow-Up**

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

- 322 • 1 month follow-up is completed at 30 days +/- 4 days from date of injury
- 323 • 3 month follow-up is completed at 90 days +/- 7 days from date of injury
- 324 • 6 month follow-up is completed at 180 days +/- 14 days from date of injury
- 325 • 12 month follow-up is completed at 360 days +/- 30 days from date of injury

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

333 migraine disorder subsequent to the mTBI, and *iii*) sustained another mTBI since the injury that they
 334 were enrolled in the study for. Furthermore, the participant's experience of ongoing mTBI
 335 symptomatology is ascertained using the *Post Concussion Symptom Scale-22 Item version (PCSS)*
 336 [82,83] at each follow-up time point, whilst quality of life is being measured using the short form of the
 337 *Quality of Life after Brain Injury (QOLIBRI-OS:[84])* at the 3-, 6-, and 12-month follow-ups.

340 **Data collection: Phase I**

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

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

347 Phase I Telephone Interview/ Questionnaire Components	
348 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	<i>PCSS</i>

349 **Data Collection: Phase II**

350 **qEEG**

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

370 **Blood-Based Biomarkers**

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

383 **Neuropsychological Assessment and Questionnaires**

1
2
3 384 Participants undergo a brief neuropsychological assessment, which is conducted by trained research
4
5 385 team members who have a postgraduate qualification in psychology, under the supervision of a clinical
6
7 386 neuropsychologist (CP). The ability to assess a broad range of cognitive domains and executive
8
9 387 functions known to be affected by mTBI in a timely manner was the primary driver for the selection of
10
11 388 tests comprising the neuropsychological testing battery. More specifically, the *Repeated Battery for the*
12
13 389 *Assessment of Neuropsychological Status Update (RBANS® Update)*[87] is being used to measure
14
15 390 immediate and delayed memory, visuospatial constructional skills, language and attention, while the
16
17 391 *Trail Making Test Forms A and B* [88] are being used to measure components of executive function.
18
19 392 Effort is also measured using the *Rey Memory Test* [89]. In addition, participants complete a battery of
20
21 393 questionnaires to assess mTBI symptomatology (*PCSS*): [82,83]), psychological distress (*Depression*
22
23 394 *Anxiety and Stress Scales-21 item version*: [90], and *Brief Symptoms Inventory-18 item version* [91]),
24
25 395 resilience (*Brief Resilience Scale*: [92]) and coping style (*Utrecht Coping List*: [93,94]). The
26
27 396 neuropsychological assessment and questionnaires are both completed in a private room, and in
28
29 397 accordance with standard neuropsychological testing arrangements, with administration time typically
30
31 398 taking 30-40 minutes. Diagnosis of PPCS will be made on the basis of a moderate-to-severe score on
32
33 399 the *PCSS* scale in line with best practice guidelines.

400

401 **Buffalo Concussion Bike Test**

402 Participants undergo exercise tolerance testing using the *Buffalo Concussion Bike Test (BCBT)* as
403
404 outlined by Haider and colleagues [95] which involves graded exertion on a recumbent bicycle
405
406 ergometer (Monark RT2, Monark Exercise, Vansbro, Sweden). Prior to conducting the test, participants
407
408 are screened using the *Physical Activity Readiness Questionnaire (PAR-Q)* [96] to assess for pre-
409
410 existing cardiac issues or increased risk for cardiopulmonary disease, orthopaedic issues or injuries that
411
412 may limit their ability to cycle, as well as other medical issues that may impede their ability to complete
413
414 the exercise test safely. Participants are then asked to rate their current symptoms at rest on a 0 to 10
415
416 point visual analogue scale (VAS), and the test is not conducted if their score is 5/10 or more at rest.
417
418 Heart rate (HR) at rest is determined after five minutes of quiet sitting using a Polar OH1+ armband
419
420 (Polar Electro Oy, Kempele, Finland). During the test, the participant is asked to maintain a set
421
422 workload as calculated by a pre-determined formula based upon body weight [95]. Exercise intensity
423
424 is increased every two minutes by increasing the required workload. HR, rating of perceived exertion
425
426 (RPE) and symptom exacerbation are also monitored and documented at the end of each stage. RPE is
427
428 determined using a modified Borg scale, which records an individual's subjective level of exertion on
429
430 a scale of 6 to 20 [97], and symptom levels on a VAS of 0 to 10 are also recorded. The criteria for
431
432 ceasing the test include: *i*) symptom exacerbation of more than two points from the pre-exercise value
433
434 (including an increase in current symptoms or the appearance of a new symptom), *ii*) voluntary
435
436 exhaustion as ascertained by a RPE exceeding 17, *iii*) judgement by the researcher that the participant

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

422

423 **Vestibular/Ocular Motor Screening (VOMS) Assessment**

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

434

435 **Magnetic Resonance Imaging (MRI)**

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

440

441 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-Labeling (pcASL)	Cerebral blood flow
Diffusion Weighted Imaging (DWI)	White matter microstructure

442

443

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

448

449

450

1
2
3 448**449 Brain morphometry**

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

455

456 Quantitative Susceptibility Mapping

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

463

464 Resting state functional MRI

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

469

470 Pseudo-continuous Arterial Spin Labelling

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

475

476 Diffusion MRI

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

484

1
2
3 485 **Clinical notification:** All MRI scans are reported by a neuroradiologist with medically relevant
4 486 incidental findings communicated to the participant's nominated GP.

5
6 487

7
8 488

9 489 **General Data Management Plan**

10
11 490 *CREST*'s study design requires data collection using various media, including electronic and paper
12 491 formats. Data acquired electronically (e.g. *Phase I* telephone interview) are being entered directly into
13 492 a secure, encrypted REDCap® [103,104] database hosted by Curtin University. Paper copies of
14 493 participant's personal information (e.g. PRF, results from *Phase II* components) are stored securely in
15 494 a locked filing cabinet at the research office, and are also digitised and uploaded to REDCap® for
16 495 storage. Imaging data (i.e. qEEG, MRI) are being organised according to the BIDS and are stored on a
17 496 secure, cloud-based storage platform also provided by Curtin University, as well as on securely stored
18 497 physical hard drives for long-term storage.

19
20 498

21 499 Upon enrolment into the study, all participants are assigned a unique identification number, and all data
22 500 that are collected from participants are identified by this number. A master list containing select
23 501 identifying information is securely stored on an encrypted server, and is available only to authorised
24 502 research staff. All identifiable information accrued for the purpose of the research study is treated as
25 503 strictly confidential, and will only be disclosed with permission from participants or as required by law.
26 504 In line with WA Health guidelines, all research data will be retained for at least seven years.

27
28 505

29
30 506

31 507 **Data Analysis Plan**

32 508 This is the first registry of its kind in WA. As such there is no existing data from which to extrapolate
33 509 power for calculations. Baseline characteristics will be compared using Chi-square tests for categorical
34 510 variables and t-tests for continuous variables, with respect to outcome (PPCS or no PPCS). Standard
35 511 regression modelling will be used to build best-performing prediction models for each of the outcomes
36 512 of interest, using principal component analysis to identify the most promising predictive indicators to
37 513 include in the model. Multiple measures of model performance, including calibration and
38 514 discrimination as well as novel measures employing reclassification tables and net reclassification
39 515 improvement will be used to establish the best and most parsimonious prediction model.

40
41 516

42
43 517

44 518 **Ethics and Dissemination**

45 519 Ethics approval for the study has been directly obtained from the Human Research Ethics Committees
46 520 (HRECs) at all of the institutions involved in the study, or where applicable, reciprocal approval has
47 521 been granted. Informed verbal consent is obtained from all participants over the telephone as part of

1
2
3 522 enrolment into the study, before data is collected in *Phase I*. Participants are provided with a copy of
4 their verbal consent and study information documentation *via* email following the *Phase I* interview.
5 523
6 524 Written consent is also sought from those participants partaking in *Phase II* prior to the undertaking of
7
8 525 any testing components. All data and samples are managed entirely anonymously with the exception of
9
10 526 the required information for follow-up telephone calls. There are few significant risks to the participants
11
12 527 in this study, and for those that have been identified, appropriate protocols have been devised which
13
14 528 have been approved by the HRECs. Participants can withdraw from the study at any time and this will
15
16 529 not have any impact on their clinical care. Data contributed to the study can also be withdrawn upon
17
18 530 request. The results of this study will be published in peer-reviewed journals and presented at local,
19
20 531 domestic and international scientific meetings. No identifiable information will be published, unless
21
22 532 permission has been obtained from participants to do so.
23
24 533
25
26 534

24 535 **Discussion**

25 536 Relative to studies previously conducted in the field, two main advantages distinguish the *CREST* study
26
27 537 by design to provide superior insight into the recovery trajectory of individuals sustaining an mTBI.
28
29 538 First: *CREST* is recruiting widely from a number of different clinical and community-based sources,
30
31 539 with scope to recruit from regional/rural and remote areas in future. Not only will this facilitate the
32
33 540 simultaneous observation of recovery trajectories associated with a variety of different mTBI injury
34
35 541 mechanisms, but it will also provide insight into whether some factors may be more salient for recovery
36
37 542 following mTBI due to different causal mechanisms. This unique recruitment approach will also
38
39 543 provide much needed data regarding the circumstances under which mTBI occurs within WA as well
40
41 544 as the incidence and prevalence of both mTBI and PPCS that may ensue, for which data is severely
42
43 545 limited. Second: *CREST* utilises an extensive testing battery that comprises a broad range of both novel
44
45 546 and established predictors of PPCS. This in itself is significant for several reasons: First and foremost,
46
47 547 such an approach will enable the evaluation of previously identified factors in a novel, community based
48
49 548 cohort that has been followed-up over a prolonged period of time. Furthermore, it features several novel
50
51 549 techniques (e.g. QSM, qEEG, metabolomics, proteomics) that have received limited attention and
52
53 550 others (e.g. exercise tolerance) that have been investigated only in specific populations (e.g. adolescent
54
55 551 athletes), expounding the utility of such methods. The systematic approach adopted by *CREST* in which
56
57 552 data is being collected also creates a fertile setting for the examination of novel or poorly investigated
58
59 553 relationships between different clinical parameters predictive of poor outcome (e.g. congruency
60
554 between qEEG and rs-fMRI; ASL and exercise tolerance), and provides opportunity for economic
555
556 555 evaluation of diagnostic and prognostic methods from both the healthcare and consumer perspectives.
557
558 556 Taken together, this research has the potential to empower clinicians and researchers alike by
559
560 557 identifying factors that may contribute to the development of an optimal ‘suite’ of rapidly deployable
558
559 558 predictive variables for the early identification of PPCS risk. It also has the potential to assist with the

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

For peer review only

561 **References**

- 562 1 NSW Ministry of Health. Adult trauma clinical practice guidelines: initial management of
563 closed head injury in adults. Sydney, NSW: 2011.
- 564 2 National Center for Injury Prevention and Control. Report to Congress on Mild Traumatic
565 Brain Injury in the United States: Steps to prevent a serious public health problem. Atlanta
566 (GA): 2003.
- 567 3 American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. *J*
568 *Head Trauma Rehabil* 1993;**8**:86–7.
- 569 4 King N. Literature review Mild head injury : Neuropathology, sequelae, measurement and
570 recovery. *Br J Clin Psychol* 1997;**36**:161–84. doi:10.1111/j.2044-8260.1997.tb01405.x
- 571 5 Pardini D, Stump J, Lovell M., *et al.* The Post-Concussion Symptom Scale (PCSS): A factor
572 analysis. *Br J Sports Med* 2004;**38**:654–64.
- 573 6 Faul M, Xu L, Wald MM, *et al.* Traumatic brain injury in the United States: emergency
574 department visits, hospitalizations and deaths 2002–2006. *US Dep Heal Hum Serv Centers Dis*
575 *Control Prev Natl Cent Inj Prev Control* 2010;**113**:399–400. doi:10.3171/2009.10.JNS091500
- 576 7 Carroll LJ, Cassidy JD, Cancelliere C, *et al.* Systematic review of the prognosis after mild
577 traumatic brain injury in adults: Cognitive, psychiatric, and mortality outcomes: Results of the
578 international collaboration on mild traumatic brain injury prognosis. *Arch. Phys. Med.*
579 *Rehabil.* 2014;**95**:S152–73. doi:10.1016/j.apmr.2013.08.300
- 580 8 Covassin T, Moran R, Wilhelm K. Concussion symptoms and neurocognitive performance of
581 high school and college athletes who incur multiple concussions. *Am J Sports Med*
582 2013;**41**:2885–9. doi:10.1177/0363546513499230
- 583 9 McCrea M, Guskiewicz K, Randolph C, *et al.* Incidence, clinical course, and predictors of
584 prolonged recovery time following sport-related concussion in high school and college
585 athletes. *J Int Neuropsychol Soc* 2013;**19**:22–33. doi:10.1017/S1355617712000872
- 586 10 McCrory P, Johnston K, Meeuwisse W, *et al.* Summary and agreement statement of the 2nd
587 International Conference on Concussion in Sport, Prague 2004. *Br J Sports Med* 2005;**39**:196–
588 204. doi:10.1136/bjism.2005.018614
- 589 11 Rabinowitz AR, Fisher AJ. Person-Specific Methods for Characterizing the Course and
590 Temporal Dynamics of Concussion Symptomatology: A Pilot Study. *Sci Rep* 2020;**10**:1248.
591 doi:10.1038/s41598-019-57220-1
- 592 12 Silverberg ND, Iaccarino MA, Panenka WJ, *et al.* Management of Concussion and Mild
593 Traumatic Brain Injury: A Synthesis of Practice Guidelines. *Arch Phys Med Rehabil* Published
594 Online First: October 2019. doi:10.1016/j.apmr.2019.10.179
- 595 13 McCrory P, Meeuwisse W, Dvořák J, *et al.* Consensus statement on concussion in sport—the
596 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports*
597 *Med* 2017;**51**:838–47. doi:10.1136/bjsports-2017-097699
- 598 14 Iverson GL, Lange RT. Post-Concussion Syndrome. In: Schoenberg M., Scott J., eds. *The*
599 *Little Black Book of Neuropsychology: A Syndrome-Based Approach*. New York: : Springer
600 2011. 745–63. doi:10.1007/978-0-387-76978-3_24
- 601 15 Cooksley R, Maguire E, Lannin NA, *et al.* Persistent symptoms and activity changes three
602 months after mild traumatic brain injury. *Aust Occup Ther J* 2018;**65**:168–75.
603 doi:10.1111/1440-1630.12457
- 604 16 Chu SY, Tsai YH, Xiao SH, *et al.* Quality of return to work in patients with mild traumatic
605 brain injury: a prospective investigation of associations among post-concussion symptoms,
606 neuropsychological functions, working status and stability. *Brain Inj* 2017;**31**.
607 doi:10.1080/02699052.2017.1332783
- 608 17 Holmes A, Chen Z, Yahng L, *et al.* Return to Learn: Academic Effects of Concussion in High
609 School and College Student-Athletes. *Front Pediatr* 2020;**8**. doi:10.3389/fped.2020.00057
- 610 18 Cancelliere C, Hincapié CA, Keightley M, *et al.* Systematic review of prognosis and return to
611 play after sport concussion: Results of the international collaboration on mild traumatic brain
612 injury prognosis. *Arch. Phys. Med. Rehabil.* 2014;**95**:S210–29.
613 doi:10.1016/j.apmr.2013.06.035
- 614 19 Zumstein MA, Moser M, Mottini M, *et al.* Long-Term Outcome in Patients With Mild

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 615 Traumatic Brain Injury: A Prospective Observational Study. *J Trauma Inj Infect Crit Care* 2011;**71**:120–7. doi:10.1097/TA.0b013e3181f2d670
- 616
- 617 20 Andersson EE, Bedics BK, Falkmer T. Mild traumatic brain injuries: A 10-year follow-up. *J Rehabil Med* 2011;**43**:323–9. doi:10.2340/16501977-0666
- 618
- 619 21 Deb S, Lyons I, Koutzoukis C. Neuropsychiatric sequelae one year after a minor head injury. doi:10.1136/jnnp.65.6.899
- 620
- 621 22 Emanuelson I, Andersson Holmkvist E, Björklund R, *et al.* Quality of life and post-concussion symptoms in adults after mild traumatic brain injury: a population-based study in western Sweden. *Acta Neurol Scand* 2003;**108**:332–8. doi:10.1034/j.1600-0404.2003.00155.x
- 622
- 623
- 624 23 King NS, Kirwilliam S. Permanent post-concussion symptoms after mild head injury. *Brain Inj* 2011;**25**:462–70. doi:10.3109/02699052.2011.558042
- 625
- 626 24 Kirsch NL, de Leon MB, Maio RF, *et al.* Characteristics of a mild head injury subgroup with extreme, persisting distress on the Rivermead Postconcussion Symptoms Questionnaire. *Arch Phys Med Rehabil* 2010;**91**:35–42. doi:10.1016/j.apmr.2009.09.019
- 627
- 628
- 629 25 Kristman VL, Côté P, Yang X, *et al.* Health care utilization of workers' compensation claimants associated with mild traumatic brain injury: A historical population-based cohort study of workers injured in 1997-1998. *Arch Phys Med Rehabil* 2014;**95**:S295–302. doi:10.1016/j.apmr.2013.08.296
- 630
- 631
- 632
- 633 26 Baugh CM, Stamm JM, Riley DO, *et al.* Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma. *Brain Imaging Behav* 2012;**6**:244–54. doi:10.1007/s11682-012-9164-5
- 634
- 635
- 636 27 Gavett BE, Stern RA, McKee AC. Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma. *Clin Sports Med* 2011;**30**:179–88. doi:10.1016/j.csm.2010.09.007
- 637
- 638
- 639 28 McKee AC, Cantu RC, Nowinski CJ, *et al.* Chronic traumatic encephalopathy in athletes: Progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol* 2009;**68**:709–35. doi:10.1097/NEN.0b013e3181a9d503
- 640
- 641
- 642 29 McKee AC, Stein TD, Nowinski CJ, *et al.* The spectrum of disease in chronic traumatic encephalopathy. *Brain* 2013;**136**:43–64. doi:10.1093/brain/aws307
- 643
- 644 30 Omalu BI, DeKosky ST, Minster RL, *et al.* Chronic traumatic encephalopathy in a National Football League Player. *Neurosurgery* 2005;**57**:128–34. doi:10.1227/01.NEU.0000163407.92769.ED
- 645
- 646
- 647 31 Stern RA, Riley DO, Daneshvar DH, *et al.* Long-term consequences of repetitive brain trauma: Chronic traumatic encephalopathy. *PM R* 2011;**3**:S460–7. doi:10.1016/j.pmrj.2011.08.008
- 648
- 649 32 Graves AB, White E, Koepsell TD, *et al.* The association between head trauma and Alzheimer's Disease. *Am J Epidemiol* 1990;**131**:491–501. doi:10.1093/oxfordjournals.aje.a115523
- 650
- 651
- 652 33 Guskiewicz KM, Marshall SW, Bailes J, *et al.* Association between Recurrent Concussion and Late-Life Cognitive Impairment in Retired Professional Football Players. *Neurosurgery* 2005;**57**:719–26. doi:10.1227/01.NEU.0000175725.75780.DD
- 653
- 654
- 655 34 Mayeux R, Ottman R, Maestre G, *et al.* Synergistic effects of traumatic head injury and apolipoprotein-epsilon4 in patients with alzheimer's disease. *Neurology* 1995;**45**:555–7. doi:10.1212/WNL.45.3.555
- 656
- 657
- 658 35 Silverberg ND, Gardner AJ, Brubacher JR, *et al.* Systematic review of multivariable prognostic models for mild traumatic brain injury. *J Neurotrauma* 2015;**32**:517–26. doi:10.1089/neu.2014.3600
- 659
- 660
- 661 36 Carroll LJ, Cassidy JD, Peloso PM, *et al.* Prognosis for mild traumatic brain injury: Results of the WHO Collaborating Centre Task Force on mild traumatic brain injury. *J Rehabil Med* 2004;**36**:84–105. doi:10.1080/16501960410023859
- 662
- 663
- 664 37 Hou R, Moss-Morris R, Peveler R, *et al.* When a minor head injury results in enduring symptoms: A prospective investigation of risk factors for postconcussional syndrome after mild traumatic brain injury. *J Neurol Neurosurg Psychiatry* 2011;**83**:217–23. doi:10.1136/jnnp-2011-300767
- 665
- 666
- 667
- 668 38 Bazarian JJ, Wong T, Harris M, *et al.* Epidemiology and predictors of post-concussive syndrome after minor head injury in an emergency population. *Brain Inj* 1999;**13**:173–89. doi:10.1080/1360788991000163407
- 669
- 669

- doi:10.1080/026990599121692
- 671 39 Lannsjö M, Backheden M, Johansson U, *et al.* Does head CT scan pathology predict outcome
672 after mild traumatic brain injury? *Eur J Neurol* 2013;**20**:124–9. doi:10.1111/j.1468-
673 1331.2012.03813.x
- 674 40 McLean SA, Kirsch NL, Tan-Schriner CU, *et al.* Health status, not head injury, predicts
675 concussion symptoms after minor injury. *Am J Emerg Med* 2009;**27**:182–90.
676 doi:10.1016/J.AJEM.2008.01.054
- 677 41 Meares S, Shores EA, Taylor AJ, *et al.* The prospective course of postconcussion syndrome:
678 The role of mild traumatic brain injury. *Neuropsychology* 2011;**25**:454–65.
679 doi:10.1037/a0022580
- 680 42 Cnossen MC, Winkler EA, Yue JK, *et al.* Development of a Prediction Model for Post-
681 Concussive Symptoms following Mild Traumatic Brain Injury: A TRACK-TBI Pilot Study. *J*
682 *Neurotrauma* 2017;**34**:2396–409. doi:10.1089/neu.2016.4819
- 683 43 Ponsford J, Willmott C, Rothwell A, *et al.* Factors influencing outcome following mild
684 traumatic brain injury in adults. *J Int Neuropsychol Soc* 2000;**6**:568–79.
685 doi:10.1017/S1355617700655066
- 686 44 Meares S, Shores EA, Taylor AJ, *et al.* Mild traumatic brain injury does not predict acute
687 postconcussion syndrome. *J Neurol Neurosurg Psychiatry* 2008;**79**:300–6.
688 doi:10.1136/jnnp.2007.126565
- 689 45 Alexander MP. Neuropsychiatric correlates of persistent postconcussive syndrome. *J Head*
690 *Trauma Rehabil* 1992;**7**:60–9. doi:10.1097/00001199-199206000-00009
- 691 46 Kashluba S, Paniak C, Casey JE. Persistent Symptoms Associated with Factors Identified by
692 the WHO Task Force on Mild Traumatic Brain Injury. *Clin Neuropsychol* 2008;**22**:195–208.
693 doi:10.1080/13854040701263655org/10.1080/13854040701263655
- 694 47 Ponsford J, Cameron P, Fitzgerald M, *et al.* Predictors of postconcussive symptoms 3 months
695 after mild traumatic brain injury. *Neuropsychology* 2012;**26**:304–13. doi:10.1037/a0027888
- 696 48 Ponsford J, Nguyen S, Downing M, *et al.* Factors associated with persistent post-concussion
697 symptoms following mild traumatic brain injury in adults. *J Rehabil Med* 2019;**51**:32–9.
698 doi:10.2340/16501977-2492
- 699 49 Thornhill S, Teasdale GM, Murray GD, *et al.* Disability in young people and adults one year
700 after head injury: prospective cohort study. *BMJ* 2000;**320**:1631–5.
701 doi:10.1136/BMJ.320.7250.1631
- 702 50 Topolovec-Vranic J, Pollmann-Mudryj MA, Ouchterlony D, *et al.* The value of serum
703 biomarkers in prediction models of outcome after mild traumatic brain injury. *J Trauma - Inj*
704 *Infect Crit Care* 2011;**71**:S478–86. doi:10.1097/TA.0b013e318232fa70
- 705 51 Roy D, Peters ME, Everett A, *et al.* Loss of consciousness and altered mental state predicting
706 depressive and post-concussive symptoms after mild traumatic brain injury. *Brain Inj*
707 2019;**33**:1064–9. doi:10.1080/02699052.2019.1606447
- 708 52 Ganti L, Khalid H, Patel PS, *et al.* Who gets post-concussion syndrome? An emergency
709 department-based prospective analysis. *Int J Emerg Med* 2014;**7**:31. doi:10.1186/s12245-014-
710 0031-6
- 711 53 Nelson LD, Furger RE, Ranson J, *et al.* Acute clinical predictors of symptom recovery in
712 emergency department patients with uncomplicated mild traumatic brain injury (mTBI) or
713 non-TBI Injuries. *J Neurotrauma* 2018;**35**:249–59. doi:10.1089/neu.2017.4988
- 714 54 King NS. Emotional, neuropsychological, and organic factors: their use in the prediction of
715 persisting postconcussion symptoms after moderate and mild head injuries. *J Neurol*
716 *Neurosurg Psychiatry* 1996;**61**:75–81. doi:10.1136/JNNP.61.1.75
- 717 55 Sheedy J, Geffen G, Donnelly J, *et al.* Emergency Department Assessment of Mild Traumatic
718 Brain Injury and Prediction of Post-Concussion Symptoms at One Month Post Injury. *J Clin*
719 *Exp Neuropsychol* 2006;**28**:755–72. doi:10.1080/13803390591000864
- 720 56 Sheedy J, Harvey E, Faux S, *et al.* Emergency department assessment of mild traumatic brain
721 injury and the prediction of postconcussive symptoms: A 3-month prospective study. *J Head*
722 *Trauma Rehabil* 2009;**24**:333–43. doi:10.1097/HTR.0b013e3181aea51f
- 723 57 Faux S, Sheedy J, Delaney R, *et al.* Emergency department prediction of post-concussive
724 syndrome following mild traumatic brain injury: An international cross-validation study. *Brain*

- 1
2
3 725 *Inj* 2011;**25**:14–22. doi:10.3109/02699052.2010.531686
- 4 726 58 Binder LM, Rohling ML, Larrabee GJ. A review of mild head trauma. part I: Meta-analytic
5 727 review of neuropsychological studies. *J Clin Exp Neuropsychol* 1997;**19**:421–31.
6 728 doi:10.1080/01688639708403870
- 7 729 59 Reitan RM, Wolfson D. Emotional disturbances and their interaction with neuropsychological
8 730 deficits. *Neuropsychol Rev* 1997;**7**:3–19. doi:10.1007/BF02876970
- 9 731 60 Dikmen S, Machamer J, Temkin N. Mild Head Injury: Facts and Artifacts. *J Clin Exp*
10 732 *Neuropsychol* 2001;**23**:729–38. doi:10.1076/jcen.23.6.729.1019
- 11 733 61 Taylor AE, Cox CA, Mailis A. Persistent neuropsychological deficits following whiplash:
12 734 Evidence for chronic mild traumatic brain injury? *Arch Phys Med Rehabil* 1996;**77**:529–35.
13 735 doi:10.1016/S0003-9993(96)90290-7
- 14 736 62 Dash PK, Zhao J, Hergenroeder G, *et al.* Biomarkers for the Diagnosis, Prognosis, and
15 737 Evaluation of Treatment Efficacy for Traumatic Brain Injury. *Neurotherapeutics* 2010;**7**:100–
16 738 14. doi:10.1016/j.nurt.2009.10.019
- 17 739 63 Zetterberg H, Smith DH, Blennow K. Biomarkers of mild traumatic brain injury in
18 740 cerebrospinal fluid and blood. *Nat Rev Neurol* 2013;**9**:201–10. doi:10.1038/nrneurol.2013.9
- 19 741 64 Papa L, Ramia MM, Edwards D, *et al.* Systematic review of clinical studies examining
20 742 biomarkers of brain injury in athletes after sports-related concussion. *J Neurotrauma*.
21 743 2015;**32**:661–73. doi:10.1089/neu.2014.3655
- 22 744 65 Undén J, Ingebrigtsen T, Romner B. Scandinavian guidelines for initial management of
23 745 minimal, mild and moderate head injuries in adults: An evidence and consensus-based update.
24 746 *BMC Med* 2013;**11**:50. doi:10.1186/1741-7015-11-50
- 25 747 66 Bazarian JJ, Biberthaler P, Welch RD, *et al.* Serum GFAP and UCH-L1 for prediction of
26 748 absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study.
27 749 *Lancet Neurol* 2018;**17**:782–9. doi:10.1016/S1474-4422(18)30231-X
- 28 750 67 Meyer J, Bartolomei C, Sauer A, *et al.* The relationship between fluid biomarkers and clinical
29 751 outcomes in sports-related concussions: a systematic review. *Brain Inj* 2020;**1**:1–11.
30 752 doi:10.1080/02699052.2020.1802780
- 31 753 68 Yuh EL, Mukherjee P, Lingsma HF, *et al.* Magnetic resonance imaging improves 3-month
32 754 outcome prediction in mild traumatic brain injury. *Ann Neurol* 2013;**73**:224–35.
33 755 doi:10.1002/ana.23783
- 34 756 69 Karr JE, Iverson GL, Berghem K, *et al.* Complicated mild traumatic brain injury in older
35 757 adults: Post-concussion symptoms and functional outcome at one week post injury. *Brain Inj*
36 758 2020;**34**:26–33. doi:10.1080/02699052.2019.1669825
- 37 759 70 Ryan LM, Warden DL. Post concussion syndrome. *Int Rev Psychiatry* 2003;**15**:310–6.
38 760 doi:10.1080/09540260310001606692
- 39 761 71 Haider MN, Leddy JJ, Wilber CG, *et al.* The Predictive Capacity of the Buffalo Concussion
40 762 Treadmill Test After Sport-Related Concussion in Adolescents. *Front Neurol* 2019;**10**:395.
41 763 doi:10.3389/fneur.2019.00395
- 42 764 72 Whitney SL, Eagle SR, Marchetti G, *et al.* Association of acute vestibular/ocular motor
43 765 screening scores to prolonged recovery in collegiate athletes following sport-related
44 766 concussion. *Brain Inj* 2020;**34**:842–7. doi:10.1080/02699052.2020.1755055
- 45 767 73 Lau BC, Collins MW, Lovell MR. Sensitivity and specificity of subacute computerized
46 768 neurocognitive testing and symptom evaluation in predicting outcomes after sports-related
47 769 concussion. *Am J Sports Med* 2011;**39**:1209–16. doi:10.1177/0363546510392016
- 48 770 74 Sullivan KA, Kempe CB, Edmed SL, *et al.* Resilience and Other Possible Outcomes After
49 771 Mild Traumatic Brain Injury: a Systematic Review. *Neuropsychol. Rev.* 2016;**26**:173–85.
50 772 doi:10.1007/s11065-016-9317-1
- 51 773 75 Anderson JFI, Fitzgerald P. Associations between coping style, illness perceptions and self-
52 774 reported symptoms after mild traumatic brain injury in prospectively studied pre-morbidly
53 775 healthy individuals. *Neuropsychol Rehabil* 2020;**30**:1115–28.
54 776 doi:10.1080/09602011.2018.1556706
- 55 777 76 Kristman VL, Borg J, Godbolt AK, *et al.* Methodological issues and research
56 778 recommendations for prognosis after mild traumatic brain injury: Results of the international
57 779 collaboration on mild traumatic brain injury prognosis. *Arch. Phys. Med. Rehabil.* 2014;**95**.

- doi:10.1016/j.apmr.2013.04.026
- 781 77 Zemek R, Barrowman N, Freedman SB, *et al.* Clinical risk score for persistent postconcussion symptoms among children with acute concussion in the ED. *J Am Med Assoc* 2016;**315**:1014–25. doi:10.1001/jama.2016.1203
- 782
783
- 784 78 Australian Bureau of Statistics. 2016 Census QuickStats Perth. Aust. Bur. Stat. QuickStats. 2017. https://quickstats.censusdata.abs.gov.au/census_services/getproduct/census/2016/quickstat/5009?opendocument (accessed 23 Sep 2020).
- 785
786
- 787 79 Australian Bureau of Statistics. Greater Perth: Region Data Summary. Aust. Bur. Stat. 2016. https://itt.abs.gov.au/itt/r.jsp?RegionSummary®ion=5GPER&dataset=ABS_REGIONAL_ASGS&geoconcept=REGION&datasetASGS=ABS_REGIONAL_ASGS&datasetLGA=ABS_NRP9_LGA®ionLGA=REGION®ionASGS=REGION (accessed 23 Sep 2020).
- 788
789
- 790 80 Carroll LJ, Cassidy JD, Holm L, *et al.* Methodological issues and research recommendations for mild traumatic brain injury: The WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehabil. Med. Suppl.* 2004;:113–25.
- 791
792
793
794 doi:10.1080/16501960410023877
- 795 81 Theadom A, Barker-Collo S, Feigin VL, *et al.* The spectrum captured: A methodological approach to studying incidence and outcomes of traumatic brain injury on a population level. *Neuroepidemiology* 2012;**38**:18–29. doi:10.1159/000334746
- 796
797
- 798 82 Lovell MR, Iverson GL, Collins MW, *et al.* Measurement of symptoms following sports-related concussion: Reliability and normative data for the post-concussion scale. *Appl Neuropsychol* 2006;**13**:166–74. doi:10.1207/s15324826an1303_4
- 799
800
- 801 83 Kontos AP, Elbin RJ, Schatz P, *et al.* A revised factor structure for the post-concussion symptom scale: Baseline and postconcussion factors. *Am J Sports Med* 2012;**40**:2375–84. doi:10.1177/0363546512455400
- 802
803
- 804 84 Von Steinbüchel N, Wilson L, Gibbons H, *et al.* Quality of life after brain injury (QOLIBRI): Scale development and metric properties. *J Neurotrauma* 2010;**27**:1167–85. doi:10.1089/neu.2009.1076
- 805
806
- 807 85 Rapp PE, Keyser DO, Albano A, *et al.* Traumatic brain injury detection using electrophysiological methods. *Front Hum Neurosci* 2015;**9**:11. doi:10.3389/fnhum.2015.00011
- 808
809
- 810 86 Thatcher RW, North DM, Curtin RT, *et al.* An EEG severity index of traumatic brain injury. *J Neuropsychiatry Clin Neurosci* 2001;**13**:77–87. doi:10.1176/jnp.13.1.77
- 811
812
- 813 87 Randolph C. *Repeatable Battery for the Assessment of Neuropsychological Status: Update*. Bloomington, MN: USA: : PsychCorp 2012.
- 814
815
- 816 88 Lezak M, Howieson D, Loring D, *et al.* *Neuropsychological Assessment*. 4th ed. New York: : Oxford University Press 2004.
- 817
818
- 819 89 Rey A. *L'examen clinique en psychologie*. Paris: : Presses Universitaires de France 1964.
- 820
821
- 822 90 Lovibond SH, Lovibond PF. *Manual for the Depression and Anxiety Stress Scales*. 2nd ed. Sydney, NSW: : Psychology Foundation 1995.
- 823
824
- 825 91 Derogatis L. *BSI 18 Brief Symptom Inventory 18*. Bloomington, MN: USA: : Pearson Clinical 2001.
- 826
827
- 828 92 Smith BW, Dalen J, Wiggins K, *et al.* The Brief Resilience Scale: Assessing the Ability to Bounce Back. *Int J Behav Med* 2008;**15**:194–200. doi:10.1080/10705500802222972
- 829
830
- 831 93 Turner H, Bryant-Waugh R, Peveler R, *et al.* A Psychometric Evaluation of an English Version of the Utrecht Coping List. *Eur Eat Disord Rev* 2012;**20**:339–42. doi:10.1002/erv.2173
- 832
833
- 834 94 Schreurs PJG, Van de Willige G, Brosschot JF, *et al.* *De Utrechtse Coping Lijst. Herziene Handleiding (revised manual)*. Lisse, The Netherlands: : Swets en Zeitlinger 1993.
- 835
836
- 837 95 Haider MN, Johnson SL, Mannix R, *et al.* The Buffalo Concussion Bike Test for Concussion Assessment in Adolescents. *Sports Health* 2019;**11**:492–7. doi:10.1177/1941738119870189
- 838
839
- 840 96 Warburton DER, Jamnik VK, Bredin SSD, *et al.* Evidence-based risk assessment and recommendations for physical activity clearance: an introduction 1 This paper is one of a selection of papers published in this Special Issue, entitled Evidence-based risk assessment and recommendations for physical activity clearance, and has undergone the Journal's usual peer review process. *Appl Physiol Nutr Metab* 2011;**36**:S1–2. doi:10.1139/h11-060
- 841
842
- 843 97 Scherr J, Wolfarth B, Christle JW, *et al.* Associations between Borg's rating of perceived

- 1
2
3 835 exertion and physiological measures of exercise intensity. *Eur J Appl Physiol* 2013;**113**:147–
4 836 55. doi:10.1007/s00421-012-2421-x
- 5 837 98 Mucha A, Collins MW, Elbin RJ, *et al.* A brief vestibular/ocular motor screening (VOMS)
6 838 assessment to evaluate concussions: Preliminary findings. *Am J Sports Med* 2014;**42**:2479–86.
7 839 doi:10.1177/0363546514543775
- 8 840 99 Gorgolewski K, Burns CD, Madison C, *et al.* Nipype: A Flexible, Lightweight and Extensible
9 841 Neuroimaging Data Processing Framework in Python. *Front Neuroinform* 2011;**5**:13.
10 842 doi:10.3389/fninf.2011.00013
- 11 843 100 Kluyver T, Ragan-Kelley B, Pérez F, *et al.* Jupyter Notebooks—a publishing format for
12 844 reproducible computational workflows. In: Loizides F, Schmidt B, eds. *Positioning and Power*
13 845 *in Academic Publishing: Players, Agents and Agendas - Proceedings of the 20th International*
14 846 *Conference on Electronic Publishing, ELPUB 2016*. Amsterdam, The Netherlands: : IOS Press
15 847 2016. 87–90. doi:10.3233/978-1-61499-649-1-87
- 16 848 101 Gorgolewski KJ, Auer T, Calhoun VD, *et al.* The brain imaging data structure, a format for
17 849 organizing and describing outputs of neuroimaging experiments. *Sci Data* 2016;**3**:1–9.
18 850 doi:10.1038/sdata.2016.44
- 19 851 102 Smith SM, Jenkinson M, Johansen-Berg H, *et al.* Tract-based spatial statistics: Voxelwise
20 852 analysis of multi-subject diffusion data. *Neuroimage* 2006;**31**:1487–505.
21 853 doi:10.1016/J.NEUROIMAGE.2006.02.024
- 22 854 103 Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)-A metadata-
23 855 driven methodology and workflow process for providing translational research informatics
24 856 support. *J Biomed Inform* 2009;**42**:377–81. doi:10.1016/j.jbi.2008.08.010
- 25 857 104 Harris PA, Taylor R, Minor BL, *et al.* The REDCap consortium: Building an international
26 858 community of software platform partners. *J. Biomed. Inform.* 2019;**95**:103208.
27 859 doi:10.1016/j.jbi.2019.103208
- 28
29 860
30 861

862 Author Affiliations

- 863 ¹ Curtin Health Innovation Research Institute, Curtin University, Bentley, WA 6102, Australia
- 864 ² Perron Institute for Neurological and Translational Science, Nedlands, WA 6009, Australia
- 865 ³ School of Public Health, Curtin University, Bentley, WA 6102, Australia
- 866 ⁴ School of Surgery, The University of Western Australia, Crawley, WA 6009, Australia
- 867 ⁵ School of Psychological Science, The University of Western Australia, Crawley, WA 6009,
868 Australia
- 869 ⁶ Discipline of Exercise Science, Murdoch University, Murdoch, WA 6150, Australia
- 870 ⁷ Australian Alzheimer's Research Foundation, Nedlands, WA 6009, Australia
- 871 ⁸ School of Human Sciences, The University of Western Australia, Crawley, WA 6009, Australia
- 872 ⁹ Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, WA 6150,
873 Australia.
- 874 ¹⁰ School of Physiotherapy and Exercise Science, Curtin University, Bentley, WA 6102, Australia
- 875 ¹¹ Emergency Department, Fiona Stanley Hospital, Murdoch, WA 6150, Australia
- 876 ¹² Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research,
877 Nedlands, WA 6009, Australia
- 878 ¹³ Emergency Department, Rockingham General Hospital, Cooloongup, WA 6168, Australia
- 879 ¹⁴ Emergency Department, Joondalup Health Campus, Joondalup, WA 6027, Australia
- 880 ¹⁵ Emergency Department, Saint John of God Midland Public Hospital, Midland, WA 6056, Australia
- 881 ¹⁶ School of Medicine, The University of Notre Dame, Fremantle, WA 6959, Australia
- 882 ¹⁷ Curtin Medical School, Curtin University, Bentley, WA 6102, Australia
- 883 ¹⁸ Emergency Department, Saint John of God Murdoch Private Hospital, Murdoch, WA 6150,
884 Australia
- 885 ¹⁹ Emergency Department, Royal Perth Hospital, Perth, WA 6000, Australia
- 886 ²⁰ Royal Flying Doctor Service- Western Operations, Jandakot, WA 6164, Australia
- 887 ²¹ Emergency Department, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia
- 888 ²² Division of Emergency Medicine, School of Medicine, The University of Western Australia,
889 Crawley, WA 6009, Australia
- 890 ²³ Emergency Department, Armadale Health Service, Mount Nasura, WA 6112, Australia
- 891 ²⁴ Statewide Director of Neurosurgery Western Australia, Department of Health, Perth, WA 6000,
892 Australia
- 893 ²⁵ Head of Department, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia
- 894 ²⁶ Head of Department, Royal Perth Hospital, Perth, WA 6000, Australia
- 895 ²⁷ Head of Department, Fiona Stanley Hospital, Murdoch, WA 6150, Australia
- 896 ²⁸ Telethon Kids Institute, West Perth, WA 6005, Australia
- 897 ²⁹ Neurological Intervention and Imaging Service of Western Australia, Sir Charles Gairdner
898 Hospital, Nedlands, WA 6009, Western Australia

1
2
3 899 ³⁰ Emergency Medicine, Royal Perth Hospital, The University of Western Australia, Perth 6000,
4 Australia

5 900
6 901

7 902

8 903 **Authors' contributions** MF DF CP MB ML SZ DX conceptualised the study and participated in initial
9 study design, with assistance from AG JT ET FB AvH. AG, SCH, JT, FB and MF drafted the manuscript.
10 904 AG prepared visual content and coordinated manuscript revisions. MF DF CP MB ML SZ DX obtained
11 905 the research funding. All other authors (ET SM AR GA BS SvS PB JI TC DX SR SH GC ML MB CP
12 906 DF) contributed to study design and revisions of the manuscript.
13 907

14 908

15 909 **Funding** The funding for this research project was provided by the Neurotrauma Research Program
16 910 WA (NRP), and was funded by the State Government of Western Australia through the Department of
17 911 Health. We wish to thank the Perron Institute for Neurological and Translational Science for its support
18 912 for this research through the award of a Perron Internal Grant.

19 913

20 914 **Competing Interests** None declared.

21 915

22 916 **Patient consent for publication** Not required.

23 917

24 918 **Ethics Approval** This study protocol has been approved by the Human Research Ethics committees of
25 919 Royal Perth Hospital (#RGS0000003024), Curtin University (HRE2019-0209), Ramsay Health Care
26 920 (#2009), and St John of God Health Care (#1628).

27 921

28 922 **Provenance and peer review** Not commissioned; externally peer reviewed

29 923
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 924 **Figure Legends**
4
5 925

6 926 *Figure 1.* Map showing location of hospital emergency departments (red crosses) throughout the Greater Perth Area from
7 927 which prospective *CREST* participants are recruited, relative to the location of the *CREST* Research Hub (blue diamond). *Note:*
8 928 SJOG: Saint John of God Hospital
9 929

10 930
11 931 *Figure 2.* Flow diagram of the *CREST* study design. Participants are recruited via Hospital ED or Community-Based Pathways
12 932 using a dedicated *Participant Referral Form*. Following the receipt of a completed *Participant Referral Form*, either by email
13 933 or fax, a member of the *CREST* research team uses a dedicated mobile telephone number to contact prospective participants.
14 934 During this phone call, interested participants are briefed on the study aims and procedures, and verbal consent is obtained to
15 935 participate in the study. Following this, the *Phase I* semi-structured telephone interview is conducted and upon its conclusion
16 936 participants are asked if they also wish to participate in *Phase II* of the study. If interested, the *CREST* research team member
17 937 completes a telephone screen to assess the participant's eligibility to undertake the additional components of *Phase II*. If a
18 938 participant is deemed eligible, a testing session is organised at the *CREST* Research Hub. Both *Phase I* and *Phase II*
19 939 components are conducted within 7 days of a participant sustaining an mTBI. All participants are followed-up by telephone
20 940 interview at 1-, 3-, 6- and 12-months following the date of injury. *Note:* * Comprises the Curtin University and Perron Institute
21 941 for Neurological and Translational Science tenancies, which are located at Queen Elizabeth II Medical Centre, Nedlands (Perth,
22 942 Western Australia); †: MRI may be conducted up to 9 days following participant's mTBI; ‡: Quality of Life is assessed using
23 943 the QOLIBRI-OS at 3-, 6- and 12-month follow-ups only. Abbreviations: EDs: Emergency departments; GPs: General
24 944 practitioners; MRI: Magnetic resonance imaging; mTBI: mild traumatic brain injury; NPA: Neuropsychological assessment;
25 945 qEEG: Quantitative electroencephalography; VOMS: Vestibular/Ocular Motor Screening test; WA: Western Australia.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

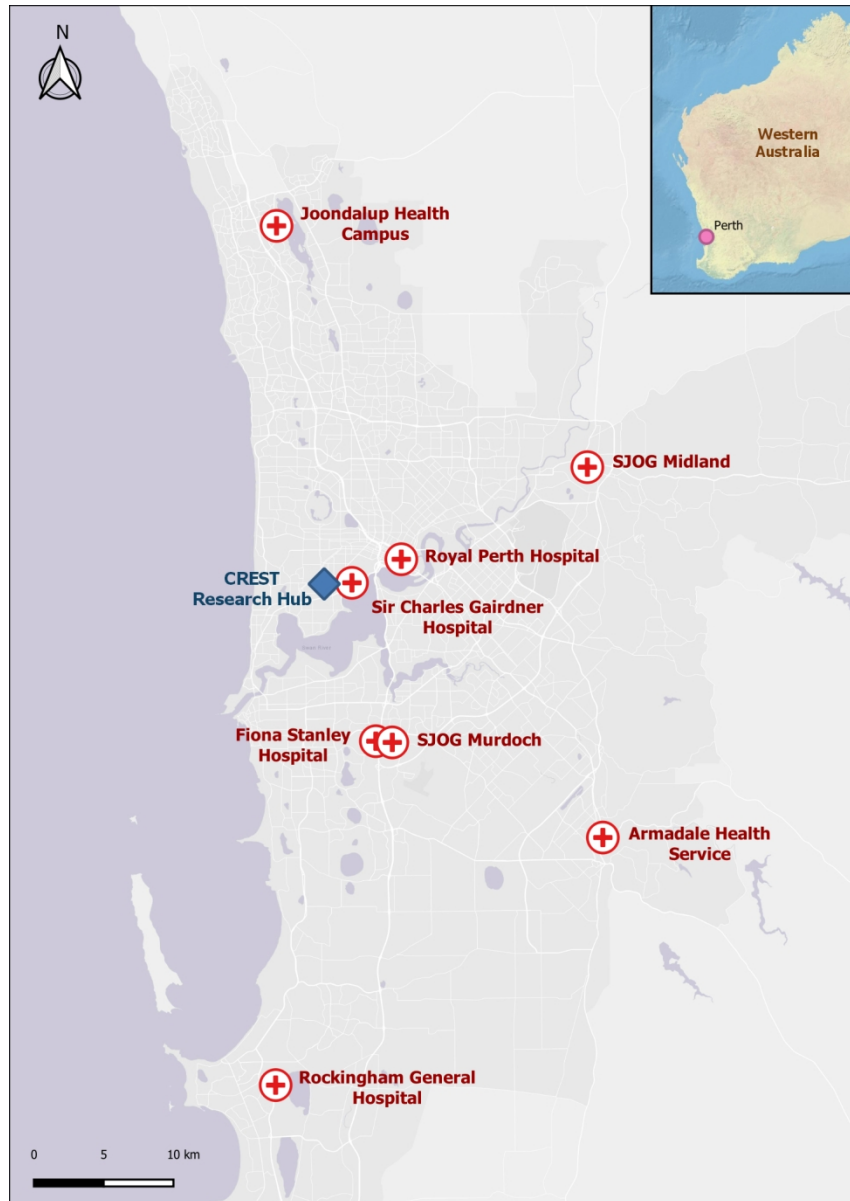


Figure 1. Map showing location of hospital emergency departments (red crosses) throughout the Greater Perth Area from which prospective CREST participants are recruited, relative to the location of the CREST Research Hub (blue diamond). Note: SJOG: Saint John of God Hospital

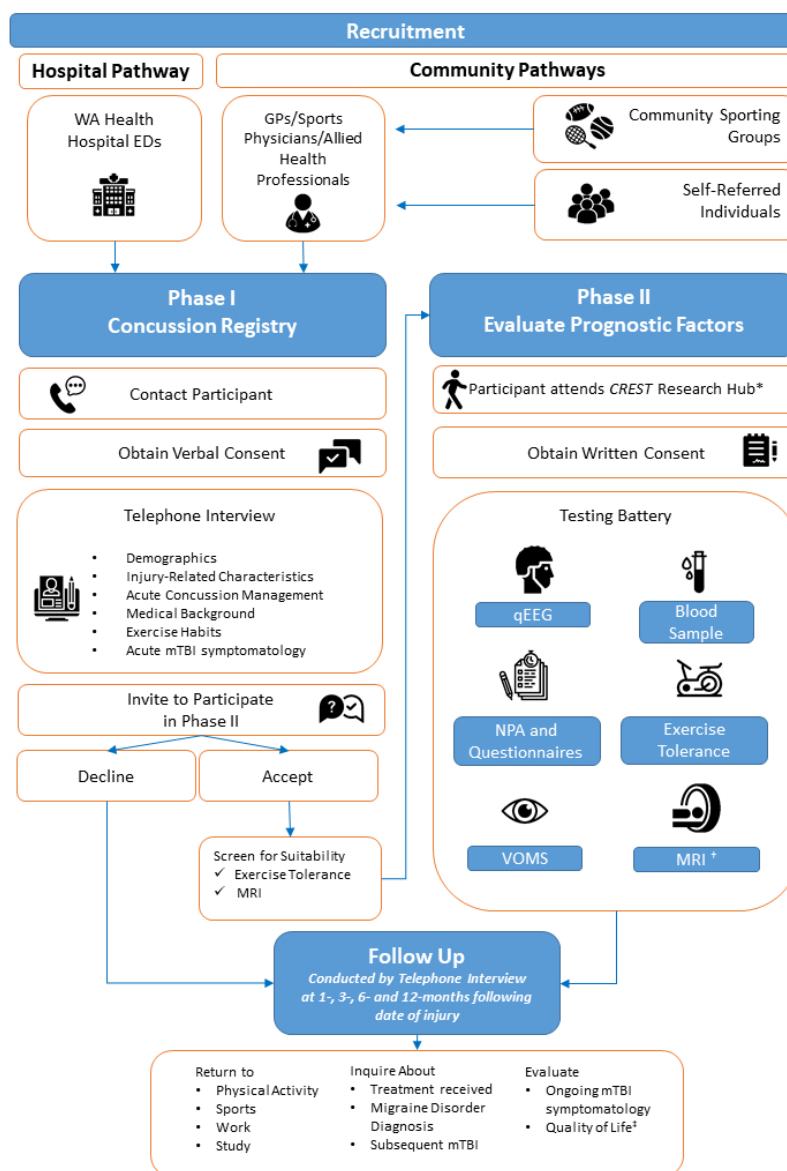


Figure 2. Flow diagram of the CREST study design. Participants are recruited via Hospital ED or Community-Based Pathways using a dedicated Participant Referral Form. Following the receipt of a completed Participant Referral Form, either by email or fax, a member of the CREST research team uses a dedicated 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

190x275mm (96 x 96 DPI)

BMJ Open: first published as 10.1136/bmjopen-2020-046460 on 13 May 2021. Downloaded from <http://bmjopen.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

1
2
3 **Predicting Outcome Following Mild Traumatic Brain Injury: Protocol for the**
4 **Longitudinal, Prospective, Observational Concussion Recovery**
5 **(CREST) Cohort Study**
6
7
8
9

10
11 **Gozt, AK et al.**
12
13

14
15
16 **Supplementary information**
17
18

- 19
20 1. Document 1. Participant site referral form.
21 2. Figure 1. The 10-20 International system of EEG electrode placement.
22 3. Table 1. MRI scan parameters.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Supplementary Document 1. Participant referral form



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, foginess) that may or may not be transient?

Please forward the completed form to:

concussionstudy@curtin.edu.au

or

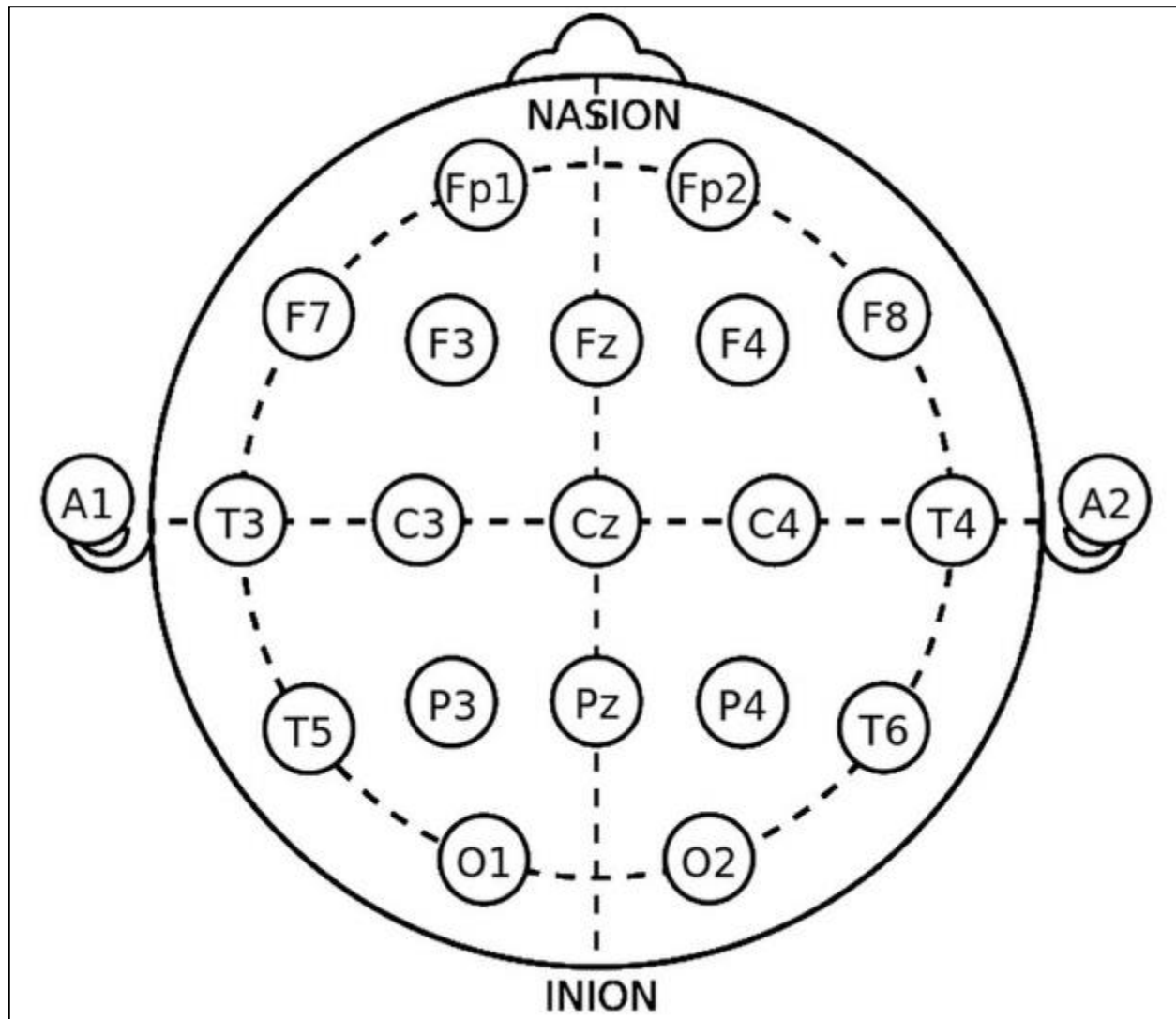
Secure e-fax 08 6270 5470

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]

1136/bmjopen-2020-046450 on 18 May 2021. Downloaded from <http://bmjopen.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

Supplementary Table 1. MRI scan parameters.

<i>Sequence</i>	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 Δ 7.7	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/mm²) [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

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-046460.R1
Article Type:	Protocol
Date Submitted by the Author:	31-Mar-2021
Complete List of Authors:	<p>Gozt, Aleksandra; Curtin University Faculty of Health Sciences, Curtin Health Innovation Research Institute; Perron Institute of Neurological and Translational Science</p> <p>Hellewell, Sarah; Curtin University Faculty of Health Sciences, Curtin Health Innovation Research Institute</p> <p>Thorne, Jacinta; Curtin University Faculty of Health Sciences, Curtin Health Innovation Research Institute</p> <p>Thomas, Elizabeth; Curtin University, Centre for Clinical Research Excellence, School of Public Health; The University of Western Australia, Division of Surgery, Faculty of Health & Medical Sciences</p> <p>Buhagiar, Francesca; The University of Western Australia Faculty of Science, School of Psychological Science</p> <p>Markovic, Shaun; Murdoch University, Discipline of Exercise Science; Australian Alzheimer's Research Foundation</p> <p>Van Houselt, Anoek; The University of Western Australia Faculty of Science, School of Human Sciences</p> <p>Ring, Alexander; Murdoch University, Institute for Immunology and Infectious Diseases; Curtin University Faculty of Health Sciences, School of Physiotherapy and Exercise Science</p> <p>Arendts, Glenn; Fiona Stanley Hospital, Emergency Department; Harry Perkins Institute of Medical Research, Centre for Clinical Research in Emergency Medicine</p> <p>Smedley, Benjamin; Rockingham General Hospital, Emergency Department</p> <p>Van Schalkwyk, Sjinene; Joondalup Health Campus, Emergency Department</p> <p>Brooks, Philip; Saint John of God Midland Public Hospital, Emergency Department; School of Medicine, The University of Notre Dame and Curtin Medical School, Curtin University</p> <p>Illiff, John ; Saint John of God Hospital Murdoch, Emergency Department; Royal Perth Hospital, Emergency Department</p> <p>Celenza, Antonio; Sir Charles Gairdner Hospital, Emergency Department; The University of Western Australia, Division of Emergency Medicine, School of Medicine</p> <p>Mukherjee, Ashes; Armadale Health Service, Emergency Department</p> <p>Xu, Dan; Curtin University Bentley Campus, Centre for Clinical Research Excellence, School of Public Health</p> <p>Robinson, Suzanne; Curtin University Faculty of Health Sciences, School of Public Health</p>

	Honeybul, Stephen; Department of Health Government of Western Australia, Statewide Director of Neurosurgery; Sir Charles Gairdner Hospital, Royal Perth Hospital and Fiona Stanley Hospital, Head of Department Cowen, Gill; Curtin University, Curtin Medical School Licari, Melissa; Telethon Kids Institute; The University of Western Australia Faculty of Science, School of Human Sciences Bynevelt, Michael; The University of Western Australia, Division of Surgery, School of Medicine; The Neurological Intervention & Imaging Service of Western Australia at Sir Charles Gairdner Hospital Pestell, Carmela; The University of Western Australia Faculty of Science, School of Psychological Science; Curtin University Faculty of Health Sciences, Curtin Health Innovation Research Institute Fatovich, Daniel; The University of Western Australia, Emergency Medicine, Royal Perth Hospital; Harry Perkins Institute of Medical Research, Centre for Clinical Research in Emergency Medicine Fitzgerald, Melinda; Curtin University Faculty of Health Sciences, Curtin Health Innovation Research Institute; Perron Institute for Neurological and Translational Sciences
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

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 1 Predicting Outcome Following Mild Traumatic Brain Injury: Protocol for the Longitudinal,
4
5 2 Prospective, Observational Concussion Recovery (*CREST*) Cohort Study
6
7 3

8 4 Aleksandra Gozt^{1,2}, Sarah C. Hellewell¹, Jacinta Thorne¹, Elizabeth Thomas^{3,4}, Francesca Buhagiar⁵,
9 5 Shaun Markovic^{6,7}, Anoenk van Houselt⁸, Alexander Ring^{9,10}, Glenn Arendts^{11,12},
10 6 Benjamin Smedley¹³, Sjinene van Schalkwyk¹⁴, Philip Brooks^{15,16,17} John Iliff^{17,18,19,20},
11 7 Antonio Celenza^{21,22}, Ashes Mukherjee²³, Dan Xu^{3,17,31}, Suzanne Robinson³,
12 8 Stephen Honeybul^{24,25,26,27}, Gill Cowen¹⁷, Melissa Licari^{8,28}, Michael Bynevelt^{4,29},
13 9 Carmela Pestell^{1,5}, Daniel Fatovich^{12,30}, Melinda Fitzgerald^{1,2}
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37

38 23 Corresponding Author:

39 24 Melinda Fitzgerald

40 25 Curtin University/Perron Institute for Neurological and Translational Science

41 26 8 Verdun Street, Nedlands, WA 6009, Australia

42 27 Email: lindy.fitzgerald@curtin.edu.au
43
44
45
46
47
48

49 30 Abstract word count: 300 words

50 31 Word count: 6389 words

51 32 Figures: 2

52 33 Tables: 3

53 34 Supplementary items: 3
54
55
56
57
58
59
60

1
2
3 **Abstract**

4 **Introduction** Mild traumatic brain injury (mTBI) is a complex injury with heterogeneous physical,
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

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

65 **Strengths and limitations of this study**

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

81 **Introduction**

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

89
90 The prevailing notion of mTBI recovery trajectory implies that symptomatic resolution can be expected
91 within approximately two weeks of injury [7–10]. However, it is increasingly realised that recovery is
92 complex and multifactorial [11], and this recovery trajectory which has been previously defined in the
93 literature pertaining to young sportspeople may not necessarily reflect recovery across age, sex, and
94 socioeconomic status. It frequently is cited that 10-20% of individuals who sustain a mTBI will
95 experience symptoms at least 1 month following injury [12], known as persistent post-concussion
96 symptoms (PPCS)[13]. Determining the true prevalence of PPCS has been complicated by the lack of
97 consistent follow-up across studies and the non-specific nature of the condition [14]. The multitudes of
98 documented ramifications stemming from PPCS have contributed to its status as an emergent public
99 health issue. PPCS may profoundly impact an individual’s ability to carry out activities of daily living,
100 and can result in functional consequences including delayed or reduced ability to return to work [15,16],

1
2
3 101 study [17] and playing sport [18], as well as impaired satisfaction and quality of life [19–22].
4 102 Furthermore, PPCS has been linked with heightened use of healthcare services [23–25], making it an
5 103 under-recognised economic burden.
6
7
8 104

9 105 It is not currently possible to identify which individuals will experience delayed recovery at the time of
10 106 mTBI diagnosis, nor is there a consensus on how to manage patients who experience such a debilitating
11 107 constellation of symptoms. The ability to predict who will develop PPCS would be of great benefit.
12 108 From a clinical perspective, a prognostic model would assist with decision-making and management of
13 109 patient expectations about their recovery. Importantly, it would enable the provision of personalised
14 110 healthcare to patients by facilitating triage to the most appropriate forms of treatment according to
15 111 individual needs *before* symptoms become chronic, thereby potentially resulting in improved patient
16 112 outcomes. Researchers would also benefit from prognostic models, which could be utilised to enrich
17 113 clinical trials for evidence-based treatments, which aim to prevent or ameliorate the effects of PPCS or
18 114 other late-stage conditions associated with mTBI, such as Chronic Traumatic Encephalopathy [26–31]
19 115 or Alzheimer’s disease [32–34].
20
21
22 116

23 117 A plethora of studies have been conducted assessing biomarkers and other factors for their capacity to
24 118 predict outcome following mTBI. However, variations in study methodologies have resulted in
25 119 inconsistent results reported in the literature [35,36], and many of the studies conducted to date have
26 120 been limited to investigating only one type or at best a small subset of prognostic factors [37].
27 121 Demographics and injury-related characteristics are amongst the most frequently examined variables,
28 122 partly because of the convenience with which they can be extracted from medical records. Factors
29 123 including female sex [38–41], previous history of mTBI [42,43], and pre-injury mental health issues
30 124 [41,43–48] have all been flagged as potential predictors of PPCS, while others such as age [49],
31 125 educational status [40,42,50], loss of consciousness [35,48,50,51] and (post-traumatic) amnesia
32 126 [35,42,52–54] are contentious and require further and more thorough investigation. Reports of poor
33 127 cognitive function following mTBI has led to the investigation of individual performance on
34 128 neuropsychological tests as a potential predictor of PPCS. A heightened risk of PPCS has been found
35 129 amongst individuals who perform poorly on post-mTBI tests of executive function [54], memory
36 130 [38,55–57] and psychomotor function [53], however, the overall fidelity with which
37 131 neuropsychological measures alone can prognosticate PPCS has been called into question given that
38 132 individual performance can be influenced by extraneous factors such as age, prior education, and socio-
39 133 economic status [58–61]. Consequently, efforts have turned towards identifying and examining other
40 134 markers of PPCS. Blood-based biomarkers are one viable option that has been embraced by the research
41 135 community, as they can be a relatively inexpensive and rapid way of assessing the physiological
42 136 mechanisms that underpin conditions of interest. To date, a vast array of candidate biomarkers
43 137 pertaining to cellular structural or functional damage as well as the biochemical and molecular

1
2
3 138 secondary injury cascades have been investigated for their ability to predict outcome after traumatic
4
5 139 brain injury [62–64]. While biomarkers such as S100B [65] and the combination of glial fibrillary acidic
6
7 140 protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) [66] have been proposed to assist
8
9 141 with clinical decision making processes relating to traumatic brain injury, studies specifically assessing
10
11 142 the relationship between fluid biomarkers and clinical outcome following mTBI have generally yielded
12
13 143 small or variable effects [67]. More recently, a host of neuroimaging techniques (e.g. MRI [68], CT
14
15 144 [69], PET [70]) and physiological biomarkers (e.g. exercise tolerance [71], vestibular/ocular function
16
17 145 [72], psychomotor responses [73]) have also been identified as having the potential to serve as objective
18
19 146 markers of PPCS, however, investigations into their prognostic capabilities have yielded inconsistent
20
21 147 results and/or been relatively limited, and thus their utility remains to be ascertained. Similarly, the
22
23 148 potential for personal predispositions (e.g. resilience [74], coping style [75]) to influence outcome
24
25 149 following injury has also been acknowledged, but more research is needed to elucidate the extent of
26
27 150 involvement.

28
29 151
30
31 152 Considering that a single predictive variable is unlikely to be the ‘silver bullet’ that predicts outcome at
32
33 153 the level of the individual [35], it is not altogether surprising that research is yet to accurately identify
34
35 154 which individuals will experience PPCS. It is increasingly recognised that a more fruitful approach
36
37 155 would draw from multiple assessment elements for multivariate prognostic modelling to better calibrate
38
39 156 the risk of poor clinical outcomes [35]. No study to date has successfully developed a prediction model
40
41 157 that is targeted specifically for prediction of individual patient outcomes following mTBI [35,76].
42
43 158 Efforts to develop validated and pragmatic tools for use in a clinical and/or research context have been
44
45 159 impeded by considerable variation between studies and use of suboptimal methodologies across studies
46
47 160 [12,76]. Common limitations identified include small and/or selected sample sizes (often resulting from
48
49 161 the use of a single centre), recruitment of participants beyond the acute injury period or across a wide
50
51 162 post-injury timespan, inconsistencies in definition and measurement of PPCS as well as variable follow-
52
53 163 up time points [35,76,77]. Furthermore, prognostic models arising from retrospective study cohorts
54
55 164 often encounter additional issues including poor data quality, missing data, minimal use of validated
56
57 165 symptom scoring scales, and lack of standardised acute evaluations [77].

58
59 166
60
61 167 The Concussion Recovery Study (*CREST*) is a large, cross-institutional study conducted in Perth,
62
63 168 Western Australia (WA), developed with the aim of identifying individuals that are at an increased risk
64
65 169 of developing PPCS. Approximately 2.4 million people reside in WA, of which 79% live within the
66
67 170 capital city of Perth [78]; the most isolated capital city in the world. The greater Perth area extends a
68
69 171 distance of over 125km, occupies an area of 6418 km² [79], and is served by 10 Emergency Departments
70
71 172 (EDs: 1 private and 9 public, of which 1 is maternity and 1 is child/adolescent exclusively). *CREST* is
72
73 173 collecting longitudinal data in two phases and utilises a multivariate, ‘suite-based’ approach that
74
75 174 incorporates demographics, injury-related characteristics, neuropsychological assessment, blood-based

1
2
3 175 biomarkers, MRI, qEEG, exercise tolerance and vestibular/ocular function to develop an evidence-
4 176 based acute predictive model for PPCS. The study hypothesises that a suite of pre-injury factors and
5 177 outcome measures that are assessed during the early presentation period may be used to predict those
6 178 at risk of experiencing PPCS compared to those who recover within a typical timeframe. It is predicted
7 179 that a combination of these outcome measures will provide superior discriminatory capacity relative to
8 180 any single marker used in isolation.

181

182

183 **Objectives**

184 The primary objectives of *CREST* are:

- 185 1. To establish a large-scale clinical research dataset of adults experiencing mTBI in Western
186 Australia, in order to observe the typical pattern of recovery from mTBI and determine the
187 incidence of PPCS within the Western Australian context.
- 188 2. To identify a suite of pre-injury factors and outcome measures during the early presentation
189 period that may be used to predict those at risk of experiencing PPCS compared to those who
190 recover within a typical timeframe.

191

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

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

197

198

199 **Methods and Analysis**

200 **Patient and Public Involvement** A *Community Conversation* was held in August 2018 involving
201 clinicians and general community members with and without a history of mTBI. The conversation took
202 form of a thematic exploration of current management considerations for mTBI, assessment measures,
203 long-term prognosis and symptomatology and contributing factors to recovery. This public consultation
204 highlighted the need for research to determine the predictors for poor outcomes following mTBI and
205 growing interest in combining screening tools, radiological scans, and biological markers for predictive
206 purposes. This stakeholder group shaped the design of the study by highlighting the importance of
207 recruiting participants from the wider community, in addition to clinical populations. The clinicians
208 shaped the *CREST* study's multimodal research design. Several individuals who participated in the
209 *Community Conversation* assisted with recruitment strategies and dissemination of information,
210 although there were not asked to assess the burden of the time required to participate in the research.
211

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

<i>Phase I</i>	
Inclusion Criteria	
<ul style="list-style-type: none"> • Aged 18-65 years • mTBI within 7 days • Diagnosed with mTBI by medical practitioner 	
Exclusion Criteria	
<ul style="list-style-type: none"> • 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 	
<i>Phase II</i>	
Inclusion Criteria	
<i>In addition to Phase I Inclusion Criteria</i>	
<ul style="list-style-type: none"> • 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	
<i>In addition to Phase I Inclusion Criteria</i>	
<ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> a. Has cardiac pacemaker or pacing wire in situ 	

213 of findings.

214

215 Study Population & Recruitment Criteria

216 *CREST* aims to capture a broad cross-section of community mTBI resulting from a variety of different
217 injury mechanisms (e.g. assault, falls, sports, transport accidents, workplace incidents). Enrolment into

218 *CREST* is open to individuals aged 18 to 65 years who have sustained a medically diagnosed mTBI
219 within the last 7 days. Table 1 details additional inclusion and exclusion criteria for *Phase I* and *Phase*

220 *II* of the study. Eligibility criterion for referral to the study are straight-forward in design given that in

221 addition to traditional medical-based pathways, the study aims to recruit participants from the general

222 community, who may have a varied understanding of mTBI. We aim to enrol n = 500 participants in

223 *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*

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

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

227 **Participant Recruitment Pathways**

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

240 **Hospital ED Pathway**

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

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

252
253 Following the identification of individuals that meet the above criteria, clinicians or research staff assist
254 prospective participants to fill out the PRF -which contains the individuals' date of birth, date of injury
255 and contact details. The PRF functions as a *permission-to-contact* form that permits the hospital to
256 release the participants' contact details to the *CREST* research team. Completed PRFs are emailed or
257 faxed through to a dedicated email address, and *CREST* research team members then use a dedicated
258 mobile telephone number to contact participants within 7 days following the date of injury noted on the
259 PRF.

261 **Community Pathways**

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

1
2
3 264 recruitment streams: *i) General Practitioner (GP)/sports physicians and allied health professionals, ii)*
4 265 *Community Sports Groups* and *iii) Self-Referral*. Recruitment of prospective participants *via* the
5
6 266 community pathways largely mirrors that of the hospital ED pathway.
7
8 267

9 268 **GPs, sports physicians and allied health professionals**

11 269 Private GP practices, sports physicians and allied health professionals within the Perth metropolitan
12 270 area have been informed about the *CREST* study, either by direct in-person approach or by digital
13 271 communication (e.g. advertisement in professional association newsletters/ mailing lists, social media).
14
15 272 In this pathway, medical practitioners screen for individuals meeting the above criteria presenting at
16 273 their practices. Details of interested participants are forwarded *via* email or fax to the *CREST* Research
17 274 Team using the PRF.
18
19 275

22 276 **Community Sports Groups**

23 277 Physiotherapists, athletic trainers and medics at sports clubs approached by the *CREST* research team
24 278 screen for prospective participants using the aforementioned criteria. If a player experiences a suspected
25 279 mTBI at training or game day, they are informed of the *CREST* study by the attending first aid personnel,
26 280 who provide the prospective participant with a copy of the PRF and direct them to seek medical
27 281 confirmation of mTBI. Should they receive a diagnosis of concussion and wish to participate in the
28 282 study, individuals can self-refer to the study by contacting the *CREST* Research Team themselves *via*
29 283 telephone, email or website (<https://concussionstudy.com.au/>), or by requesting their attending medical
30 284 professional to forward the PRF to the *CREST* research team on their behalf.
31
32 285

38 286 **Self-Referral**

39 287 Individuals from the general community who have sustained an mTBI may participate in the study *via*
40 288 self-referral, and can do so by directly contacting the *CREST* Research Team *via* telephone, email, fax
41 289 or website. Individuals recruited using this pathway are asked to provide the name of the medical
42 290 professional who diagnosed them with an mTBI. In the event that prospective participants have not yet
43 291 sought medical attention by the time they make contact with the research team, individuals are requested
44 292 to first seek medical confirmation of mTBI. If prospective participants are able to meet this request and
45 293 make contact with the research team within 7 days of date of injury, they remain eligible for study
46 294 enrolment.
47
48 295

54 296 **Study Design**

55 297 *CREST* is a prospective, longitudinal observational cohort study, which follows participants over the
56 298 course of one year after their mTBI. Individuals who do not develop PPCS serve as controls, which is
57 299 in line with the study's second primary objective of identifying factors that may be able to discriminate
60 300 between individuals who do and do not follow a typical recovery trajectory following mTBI. The study

1
2
3 301 comprises of two parts, referred to as '*Phase I*' and '*Phase II*', respectively, and follow-ups conducted
4 302 at multiple time points. This study design was primarily adopted to maximise recruitment efforts. Very
5 303 little research has been conducted in WA with respect to mTBI, and this two-part approach will help
6 304 foster greater inclusivity and representation by allowing individuals to partake in the research despite
7 305 the tyranny of distance. This is particularly pertinent to individuals residing in rural and regional areas
8 306 of Western Australia, whom can be underrepresented in research studies. The inclusion of this
9 307 demographic may also provide insights into otherwise unknown factors that may influence recovery
10 308 following mTBI. Figure 2 provides a graphical depiction of study design. To assess the influence of
11 309 potential biases, a minimal screening log records basic demographic characteristics of individuals who
12 310 are referred to the study but do not meet eligibility criteria or decline participation. Furthermore, data
13 311 being collected as part of *Phase I* will elucidate any differences in the characteristics of individuals who
14 312 do and do not opt to participate in *Phase II*.

313

314

315

316 ***Phase I***

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

326

327 ***Phase II***

328 *Phase II* has been designed to serve as a comprehensive in-person battery of tests, which is also
329 completed within 7 days of date of injury for the reasons stated above. Testing takes place at the Curtin
330 University and Perron Institute for Neurological and Translational Science tenancies, which are both
331 located on the Queen Elizabeth II Medical Centre (QEIIIMC) campus in Nedlands (Perth, Western
332 Australia). During this session, qEEG is performed, a blood sample is taken, and neuropsychological,
333 exercise tolerance and vestibular/ocular function testing is conducted. *Phase II* testing typically takes
334 2.5-3 hours to complete.

335

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

1
2
3 338 the scanner that is being utilised for the purposes of the study, the MRI is often performed separately to
4
5 339 the other *Phase II* components, generally taking place afterhours or on weekends. To accommodate for
6
7 340 scanner availability, *CREST* participants may be scanned up to 9 days following the date that they
8
9 341 sustained their mTBI.
10
11 342

343

343 **Follow-Up**

12 344 Regardless of whether participants opt to complete *Phase I* only, or both *Phase I* and *Phase II*, they are
13 345 followed-up by telephone interview at 1, 3, 6 and 12 months post-injury. To ensure consistency with
14 346 follow-up timeframes, the following variations are being adhered to:

- 17 347 • 1 month follow-up is completed at 30 days +/- 4 days from date of injury
- 18 348 • 3 month follow-up is completed at 90 days +/- 7 days from date of injury
- 19 349 • 6 month follow-up is completed at 180 days +/- 14 days from date of injury
- 20 350 • 12 month follow-up is completed at 360 days +/- 30 days from date of injury

351

25 352 The purpose of the follow-up telephone interviews is to document each participant's recovery
26 353 experience following their mTBI. Thus, at each follow-up time point, information is collected about a
27 354 number of functional outcomes that may also be predicted. More specifically, these include the
28 355 individual's return to physical activity, sport, work, and study (if applicable). During the follow-up
29 356 telephone interviews, participants are also queried about whether or not they have *i*) received or are
30 357 currently seeking any ongoing allied health, alternative or medical treatments for their mTBI (e.g.
31 358 physiotherapy, psychotherapy, chiropractic or other medical treatment), *ii*) been diagnosed with a
32 359 migraine disorder subsequent to the mTBI, and *iii*) sustained another mTBI since the injury that they
33 360 were enrolled in the study for. Furthermore, the participant's experience of ongoing mTBI
34 361 symptomatology is ascertained using the *Post Concussion Symptom Scale-22 Item version (PCSS)*
35 362 [82,83] at each follow-up time point, whilst quality of life is being measured using the short form of the
36 363 *Quality of Life after Brain Injury (QOLIBRI-OS)*:[84]) at the 3-, 6-, and 12-month follow-ups.
37
38
39
40
41
42
43
44
45
46
47

364

365

366 **Study Completion**

48 367 Individual participation in the study is considered to be complete at the 12-month follow-up. At no point
49 368 is a participant considered to be discontinued (i.e. the study participants are not required to complete all
50 369 of the follow-up interviews). Research team members attempt to contact participants at each of the four
51 370 individual follow-up time points, regardless of whether or not data was collected for the preceding
52 371 follow-up time point. A participant is considered to be '*lost to follow-up*' when contact cannot be made
53 372 with a participant within the follow-up variations stated above, but only for the individual time point in
54 373 question. Inability to contact participants at follow-up does not preclude participants from participating
55
56
57
58
59
60

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

381

382 **Data collection: Phase I**

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

387

388 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

1
2
3 389
4
5 390

6 391 **Data Collection: Phase II**

8 392 **qEEG**

9 393 **EEG data acquisition and analysis** EEG acquisition is conducted using a 19-channel Electro-cap
11 394 (Electro-Cap International Inc., Eaton, Ohio: USA) and a Mitsar amplifier (Mitsar, Ltd., St Petersburg,
12 395 Russia), with quantitative and low resolution electromagnetic tomography analysis (LORETA)
14 396 conducted using NeuroGuide software (Applied Neuroscience, Inc., Florida, USA), which has been
16 397 extensively validated in the literature, including within populations with mTBI [85,86]. For scalp EEG
17 398 recording, the participant's head circumference is measured and fitted with an appropriately sized
19 399 Electro-cap, with all electrodes connected using the standard 10-20 system (See Supplementary Figure
20 400 1). Each scalp electrode is prepared by parting the hair and filling it with electroconductive gel (Electro-
22 401 Gel™, Electro-Cap International Inc, Eaton, Ohio: USA). EEG activity is recorded from 19 scalp
23 402 electrodes and impedance kept below 10 kΩ, using a linked ears montage, where the ear lobes act as a
25 403 reference. Resting state data is recorded for 10 minutes, with five-minute eyes open and eyes closed
27 404 condition blocks. Approximately 60 seconds of artefact-free data will be selected
28 405 using NeuroGuide software (Applied Neuroscience, Inc.), and individual's activity will be compared to
30 406 the software's normative database (N = 727). This comparison will provide a Traumatic Brain Injury
31 407 Index score using a TBI Discriminant Index [86], indicating the severity of the person's TBI ranging
33 408 from zero to ten (normal = 0, mild = 1 to <3, moderate = 3-5, severe = >5). LORETA analysis
34 409 and NeuroNavigator software (Applied Neuroscience, Inc., Largo, Florida: USA) will be used to
36 410 identify areas of dysfunction within networks of interest.

38 411

39 412 **Blood-Based Biomarkers**

41 413 **Blood sample collection and analysis** Trained research assistants obtain a 20mL blood sample from
42 414 non-fasting participants by venepuncture. Whole blood is collected into BD Vacutainer®
44 415 ethylenediaminetetraacetic acid (EDTA) and serum (SST) blood collection tubes, and rested at room
46 416 temperature for approximately 30 minutes before centrifugation at 3000 rpm for 10 minutes at 4°C.
47 417 Samples are then aliquoted into 250 µL vials and put into long-term storage at -80°C until analysis.
49 418 Blood samples will be analysed by a variety of methods with the intent of quantifying novel and
51 419 established fluid biomarkers that are associated with mTBI pathophysiology. In particular, protein
52 420 biomarkers pertaining to neuronal and glial structure and function (e.g. GFAP, UCH-L1), microRNAs,
54 421 genetic signatures, phenomics and metabolomics will be investigated. An additional whole blood
55 422 sample is examined using a haematology panel (Mindray BC-2800 Vet Auto Hematology Analyzer;
57 423 Shenzhen, China) to investigate differences in blood components.

58 424
59
60

425 **Neuropsychological Assessment and Questionnaires**

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

441

442 **Buffalo Concussion Bike Test**

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

1
2
3 461 is displaying visible signs of distress, or *iv*) a request by the participant to stop the test. The participant's
4 462 HR at cessation of the test is recorded as the 'HR threshold'.

5
6 463

7 464 **Vestibular/Ocular Motor Screening (VOMS) Assessment**

8 465 The VOMS assessment is a targeted test used to identify vestibular and/or ocular motor dysfunction
9 466 following mTBI as described by Mucha and colleagues [98]. Briefly, the VOMS involves examining
10 467 horizontal and vertical smooth pursuits, horizontal and vertical saccades, near point convergence
11 468 (measured in centimetres), and visual motor sensitivity. Symptoms (namely headache, dizziness, nausea
12 469 and fogginess) are monitored prior to the commencement of the test, as well as after the completion of
13 470 each task, to determine the effect of each component on symptom exacerbation. Symptoms are recorded
14 471 as a score on a VAS ranging from 0 to 10, and the test is ceased if symptoms increase by three points.
15 472 Any abnormal findings or provocation of symptoms is considered a 'positive' test, and a potential
16 473 indicator of vestibular/ocular system dysfunction. The *VOMS* takes approximately 5-10 minutes to
17 474 complete.

18 475

19 476 **Magnetic Resonance Imaging (MRI)**

20 477 **MRI Acquisition** MRI is conducted using a Philips Ingenia 3T Multi Transmit Wide Bore Scanner
21 478 (Philips Healthcare, Best, The Netherlands) equipped with a 32-channel head coil. The imaging
22 479 protocol takes approximately 50 minutes to complete and comprises standardised sequences as outlined
23 480 in Table 3.

24 481

25 482 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-Labeling (pcASL)	Cerebral blood flow
Diffusion Weighted Imaging (DWI)	White matter microstructure

26 483

27 484

28 485 **MRI Data Analysis** Custom-built automated data processing pipelines will be constructed in Python
29 486 under the Nipype framework [99] on Linux (Ubuntu 18.04 Bionic Beaver distribution) and deployed
30 487 using Jupyter Notebook [100]. Raw DICOM data are converted to NIfTI format and stored for analysis
31 488 according to the Brain Imaging Data Structure (BIDS; [101]) recommendations.

32 489

489

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, Massachusetts: USA).

496

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.

504

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.

510

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.

516

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.

525

1
2
3 526 **Clinical notification** All MRI scans are reported by a neuroradiologist with medically relevant
4 527 incidental findings communicated to the participant's nominated GP.

528

529

9 530 **General Data Management Plan**

11 531 *CREST*'s study design requires data collection using various media, including electronic and paper
12 532 formats. Data acquired electronically (e.g. *Phase I* telephone interview) are being entered directly into
13 533 a secure, encrypted REDCap® [103,104] database hosted by Curtin University, effectively serving as
14 534 a standardized case form. Paper copies of participant's personal information (e.g. PRF, results from
15 535 *Phase II* components) are stored securely in a locked filing cabinet at the research office, and are also
16 536 digitised and uploaded to REDCap® for storage. Imaging data (i.e. qEEG, MRI) are being organised
17 537 according to the BIDS and are stored on a secure, cloud-based storage platform also provided by Curtin
18 538 University, as well as on securely stored physical hard drives for long-term storage.

539

25 540 Upon enrolment into the study, all participants are assigned a unique identification number, and all data
26 541 that are collected from participants are identified by this number. A master list containing select
27 542 identifying information is securely stored on an encrypted server, and is available only to authorised
28 543 research staff. All identifiable information accrued for the purpose of the research study is treated as
29 544 strictly confidential, and will only be disclosed with permission from participants or as required by law.
30 545 In line with WA Health guidelines, all research data will be retained for at least seven years.

546

547

38 548 **Data Analysis Plan**

39 549 **PCSS Diagnosis** PPCS will be diagnosed using the *Post Concussion Symptoms Scale* (PCSS). This
40 550 questionnaire is listed as a NINDS-Common Data Element, although there are no definitive rules for
41 551 implementing a threshold for determining the presence of PPCS. As described in Alla et al., (2012)
42 552 [105], we will be applying a threshold of 6 or more for males and 7 or more for females on the PCSS.
43 553 Diagnosis of PPCS will be made at 3 months post-injury, and will be revisited independently at the 6
44 554 and 12 months follow-ups.

555

50 556 **Statistical Analysis Plan** This is the first registry of its kind in WA. There is limited existing data from
51 557 which to extrapolate power for calculations. Nevertheless, *Phase I* is considered to be appropriately
52 558 powered to detect known potentially predictive indicators from pre-injury and demographic factors.
53 559 Our data analysis plan of analysing modalities separately will ensure that *Phase II* is sufficiently
54 560 powered to detect particularly promising differences. It is acknowledged that only a select number of
55 561 variables can be included in the multivariate model, and these will be identified using regression

1
2
3 562 analyses. Only those that are identified to be most promising based on these analyses will be included
4
5 563 in the final multivariate model.

6 564 Baseline characteristics will be compared using Chi-square tests for categorical variables and t-tests for
7
8 565 continuous variables, with respect to outcome (PPCS or no PPCS). In order to identify suitable
9
10 566 indicators, each type of outcome measure will be analysed separately, and the most promising measures
11
12 567 identified. For example, each MRI modality being investigated will be analysed separately, and
13
14 568 statistical analyses will be conducted on outcomes relevant to each modality (e.g. concentrations in
15
16 569 regions of interest for particular brain structures in QSM images will be quantified and compared in
17
18 570 individuals who are 'diagnosed' with PPCS and those who are deemed to have recovered). Receiver
19
20 571 Operating Characteristic (ROC) analysis will be used to determine a discriminate index to separate
21
22 572 PPCS from typical recovery. Standard regression modelling will be used to build best-performing
23
24 573 prediction models for each of the outcomes of interest, using principal component analysis to identify
25
26 574 the most promising predictive indicators to include in the model. The most predictive outcomes for each
27
28 575 modality will be identified and can be used in multivariate modelling combining the most promising
29
30 576 outcomes from the multiple modalities. Multiple measures of model performance, including calibration
31
32 577 and discrimination as well as novel measures employing reclassification tables and net reclassification
33
34 578 improvement will be used to establish the best and most parsimonious prediction model. This could
35
36 579 help define criteria for further validation studies in future.

37
38 580 Missing data will be handled on a case-by-case basis and appropriate approaches will be implemented
39
40 581 under the guidance of a biostatistician. The study purpose is to identify predictors of PPCs at various
41
42 582 time points post-injury. An advantage of such an approach is that if certain follow-up time points are
43
44 583 missed, analysis can still proceed.

45 584

46 585

47 586 **Ethics and Dissemination**

48 587 Ethics approval for the study has been directly obtained from the Human Research Ethics Committees
49
50 588 (HRECs) at all of the institutions involved in the study, or where applicable, reciprocal approval has
51
52 589 been granted. Informed verbal consent is obtained from all participants over the telephone as part of
53
54 590 enrolment into the study, before data is collected in *Phase I*. Participants are provided with a copy of
55
56 591 their verbal consent and study information documentation *via* email following the *Phase I* interview.
57
58 592 Written consent is also sought from those participants partaking in *Phase II* prior to the undertaking of
59
60 593 any testing components. All data and samples are managed entirely anonymously with the exception of
61
62 594 the required information for follow-up telephone calls. There are few significant risks to the participants
63
64 595 in this study, and for those that have been identified, appropriate protocols have been devised which
65
66 596 have been approved by the HRECs. Participants can withdraw from the study at any time and this will
67
68 597 not have any impact on their clinical care. Data contributed to the study can also be withdrawn upon
69
70 598 request. The results of this study will be published in peer-reviewed journals and presented at local,

1
2
3 599 domestic and international scientific meetings. No identifiable information will be published, unless
4 permission has been obtained from participants to do so.

5 600
6 601

7
8 602

9 603 **Discussion**

10
11 604 Relative to studies previously conducted in the field, two main advantages distinguish the *CREST* study
12 by design to provide superior insight into the recovery trajectory of individuals sustaining an mTBI.

13 605 First: *CREST* is recruiting widely from a number of different clinical and community-based sources,
14 with scope to recruit from regional/rural and remote areas in future. Not only will this facilitate the
15 simultaneous observation of recovery trajectories associated with a variety of different mTBI injury

16 606 mechanisms, but it will also provide insight into whether some factors may be more salient for recovery
17 following mTBI due to different causal mechanisms. This unique recruitment approach will also
18 provide much needed data regarding the circumstances under which mTBI occurs within WA as well

19 607 as the incidence and prevalence of both mTBI and PPCS that may ensue, for which data is significantly
20 limited. Second: *CREST* utilises an extensive testing battery that comprises a broad range of both novel
21 and established predictors of PPCS. This in itself is significant for several reasons: First and foremost,

22 608 such an approach will enable the evaluation of previously identified factors in a novel, community based
23 cohort that has been followed-up over a prolonged period of time. Furthermore, it features several novel
24 techniques (e.g. QSM, qEEG, metabolomics, proteomics) that have received limited attention and
25 others (e.g. exercise tolerance) that have been investigated only in specific populations (e.g. adolescent

26 609 athletes), expounding the utility of such methods. The systematic approach adopted by *CREST* in which
27 data is being collected also creates a fertile setting for the examination of novel or poorly investigated
28 relationships between different clinical parameters predictive of poor outcome (e.g. congruency
29 between qEEG and rs-fMRI; ASL and exercise tolerance), and provides opportunity for economic

30 610 evaluation of diagnostic and prognostic methods from both the healthcare and consumer perspectives.
31 Taken together, this research has the potential to empower clinicians and researchers alike by
32 identifying factors that may contribute to the development of an optimal 'suite' of rapidly deployable
33 predictive variables for the early identification of PPCS risk. It also has the potential to assist with the
34 early identification of patients at risk of experiencing PPCS and enable timely patient-centred treatment,
35 and thereby help to reduce the personal, economic and societal burden of mTBI.

36 611
37 612
38 613
39 614
40 615
41 616
42 617
43 618
44 619
45 620
46 621
47 622
48 623
49 624
50 625
51 626
52 627
53 628

54
55
56
57
58
59
60

61
62
63
64
65
66
67
68
69
70

71
72
73
74
75
76
77
78
79
80

81
82
83
84
85
86
87
88
89
90

91
92
93
94
95
96
97
98
99
100

101
102
103
104
105
106
107
108
109
110

111
112
113
114
115
116
117
118
119
120

121
122
123
124
125
126
127
128
129
130

629 **References**

- 630 1 NSW Ministry of Health. Adult trauma clinical practice guidelines: initial management of
631 closed head injury in adults. Sydney, NSW: 2011.
- 632 2 National Center for Injury Prevention and Control. Report to Congress on Mild Traumatic
633 Brain Injury in the United States: Steps to prevent a serious public health problem. Atlanta
634 (GA): 2003.
- 635 3 American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. *J*
636 *Head Trauma Rehabil* 1993;**8**:86–7.
- 637 4 King N. Literature review Mild head injury : Neuropathology, sequelae, measurement and
638 recovery. *Br J Clin Psychol* 1997;**36**:161–84. doi:10.1111/j.2044-8260.1997.tb01405.x
- 639 5 Pardini D, Stump J, Lovell M., *et al.* The Post-Concussion Symptom Scale (PCSS): A factor
640 analysis. *Br J Sports Med* 2004;**38**:654–64.
- 641 6 Faul M, Xu L, Wald MM, *et al.* Traumatic brain injury in the United States: emergency
642 department visits, hospitalizations and deaths 2002–2006. *US Dep Heal Hum Serv Centers Dis*
643 *Control Prev Natl Cent Inj Prev Control* 2010;**113**:399–400. doi:10.3171/2009.10.JNS091500
- 644 7 Carroll LJ, Cassidy JD, Cancelliere C, *et al.* Systematic review of the prognosis after mild
645 traumatic brain injury in adults: Cognitive, psychiatric, and mortality outcomes: Results of the
646 international collaboration on mild traumatic brain injury prognosis. *Arch. Phys. Med.*
647 *Rehabil.* 2014;**95**:S152–73. doi:10.1016/j.apmr.2013.08.300
- 648 8 Covassin T, Moran R, Wilhelm K. Concussion symptoms and neurocognitive performance of
649 high school and college athletes who incur multiple concussions. *Am J Sports Med*
650 2013;**41**:2885–9. doi:10.1177/0363546513499230
- 651 9 McCrea M, Guskiewicz K, Randolph C, *et al.* Incidence, clinical course, and predictors of
652 prolonged recovery time following sport-related concussion in high school and college
653 athletes. *J Int Neuropsychol Soc* 2013;**19**:22–33. doi:10.1017/S1355617712000872
- 654 10 McCrory P, Johnston K, Meeuwisse W, *et al.* Summary and agreement statement of the 2nd
655 International Conference on Concussion in Sport, Prague 2004. *Br J Sports Med* 2005;**39**:196–
656 204. doi:10.1136/bjism.2005.018614
- 657 11 Rabinowitz AR, Fisher AJ. Person-Specific Methods for Characterizing the Course and
658 Temporal Dynamics of Concussion Symptomatology: A Pilot Study. *Sci Rep* 2020;**10**:1248.
659 doi:10.1038/s41598-019-57220-1
- 660 12 Silverberg ND, Iaccarino MA, Panenka WJ, *et al.* Management of Concussion and Mild
661 Traumatic Brain Injury: A Synthesis of Practice Guidelines. *Arch Phys Med Rehabil* Published
662 Online First: October 2019. doi:10.1016/j.apmr.2019.10.179
- 663 13 McCrory P, Meeuwisse W, Dvořák J, *et al.* Consensus statement on concussion in sport—the
664 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports*
665 *Med* 2017;**51**:838–47. doi:10.1136/bjsports-2017-097699
- 666 14 Iverson GL, Lange RT. Post-Concussion Syndrome. In: Schoenberg M., Scott J., eds. *The*
667 *Little Black Book of Neuropsychology: A Syndrome-Based Approach*. New York: : Springer
668 2011. 745–63. doi:10.1007/978-0-387-76978-3_24
- 669 15 Cooksley R, Maguire E, Lannin NA, *et al.* Persistent symptoms and activity changes three
670 months after mild traumatic brain injury. *Aust Occup Ther J* 2018;**65**:168–75.
671 doi:10.1111/1440-1630.12457
- 672 16 Chu SY, Tsai YH, Xiao SH, *et al.* Quality of return to work in patients with mild traumatic
673 brain injury: a prospective investigation of associations among post-concussion symptoms,
674 neuropsychological functions, working status and stability. *Brain Inj* 2017;**31**.
675 doi:10.1080/02699052.2017.1332783
- 676 17 Holmes A, Chen Z, Yahng L, *et al.* Return to Learn: Academic Effects of Concussion in High
677 School and College Student-Athletes. *Front Pediatr* 2020;**8**. doi:10.3389/fped.2020.00057
- 678 18 Cancelliere C, Hincapié CA, Keightley M, *et al.* Systematic review of prognosis and return to
679 play after sport concussion: Results of the international collaboration on mild traumatic brain
680 injury prognosis. *Arch. Phys. Med. Rehabil.* 2014;**95**:S210–29.
681 doi:10.1016/j.apmr.2013.06.035
- 682 19 Zumstein MA, Moser M, Mottini M, *et al.* Long-Term Outcome in Patients With Mild

- 1
2
3 683 Traumatic Brain Injury: A Prospective Observational Study. *J Trauma Inj Infect Crit Care*
4 684 2011;**71**:120–7. doi:10.1097/TA.0b013e3181f2d670
- 5 685 20 Andersson EE, Bedics BK, Falkmer T. Mild traumatic brain injuries: A 10-year follow-up. *J*
6 686 *Rehabil Med* 2011;**43**:323–9. doi:10.2340/16501977-0666
- 7 687 21 Deb S, Lyons I, Koutzoukis C. Neuropsychiatric sequelae one year after a minor head injury.
8 688 doi:10.1136/jnnp.65.6.899
- 9 689 22 Emanuelson I, Andersson Holmkvist E, Björklund R, *et al.* Quality of life and post-concussion
10 690 symptoms in adults after mild traumatic brain injury: a population-based study in western
11 691 Sweden. *Acta Neurol Scand* 2003;**108**:332–8. doi:10.1034/j.1600-0404.2003.00155.x
- 12 692 23 King NS, Kirwilliam S. Permanent post-concussion symptoms after mild head injury. *Brain*
13 693 *Inj* 2011;**25**:462–70. doi:10.3109/02699052.2011.558042
- 14 694 24 Kirsch NL, de Leon MB, Maio RF, *et al.* Characteristics of a mild head injury subgroup with
15 695 extreme, persisting distress on the Rivermead Postconcussion Symptoms Questionnaire. *Arch*
16 696 *Phys Med Rehabil* 2010;**91**:35–42. doi:10.1016/j.apmr.2009.09.019
- 17 697 25 Kristman VL, Côté P, Yang X, *et al.* Health care utilization of workers' compensation
18 698 claimants associated with mild traumatic brain injury: A historical population-based cohort
19 699 study of workers injured in 1997-1998. *Arch Phys Med Rehabil* 2014;**95**:S295–302.
20 700 doi:10.1016/j.apmr.2013.08.296
- 21 701 26 Baugh CM, Stamm JM, Riley DO, *et al.* Chronic traumatic encephalopathy:
22 702 neurodegeneration following repetitive concussive and subconcussive brain trauma. *Brain*
23 703 *Imaging Behav* 2012;**6**:244–54. doi:10.1007/s11682-012-9164-5
- 24 704 27 Gavett BE, Stern RA, McKee AC. Chronic Traumatic Encephalopathy: A Potential Late Effect
25 705 of Sport-Related Concussive and Subconcussive Head Trauma. *Clin Sports Med* 2011;**30**:179–
26 706 88. doi:10.1016/j.csm.2010.09.007
- 27 707 28 McKee AC, Cantu RC, Nowinski CJ, *et al.* Chronic traumatic encephalopathy in athletes:
28 708 Progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol* 2009;**68**:709–35.
29 709 doi:10.1097/NEN.0b013e3181a9d503
- 30 710 29 McKee AC, Stein TD, Nowinski CJ, *et al.* The spectrum of disease in chronic traumatic
31 711 encephalopathy. *Brain* 2013;**136**:43–64. doi:10.1093/brain/aws307
- 32 712 30 Omalu BI, DeKosky ST, Minster RL, *et al.* Chronic traumatic encephalopathy in a National
33 713 Football League Player. *Neurosurgery* 2005;**57**:128–34.
34 714 doi:10.1227/01.NEU.0000163407.92769.ED
- 35 715 31 Stern RA, Riley DO, Daneshvar DH, *et al.* Long-term consequences of repetitive brain trauma:
36 716 Chronic traumatic encephalopathy. *PM R* 2011;**3**:S460–7. doi:10.1016/j.pmrj.2011.08.008
- 37 717 32 Graves AB, White E, Koepsell TD, *et al.* The association between head trauma and
38 718 Alzheimer's Disease. *Am J Epidemiol* 1990;**131**:491–501.
39 719 doi:10.1093/oxfordjournals.aje.a115523
- 40 720 33 Guskiewicz KM, Marshall SW, Bailes J, *et al.* Association between Recurrent Concussion and
41 721 Late-Life Cognitive Impairment in Retired Professional Football Players. *Neurosurgery*
42 722 2005;**57**:719–26. doi:10.1227/01.NEU.0000175725.75780.DD
- 43 723 34 Mayeux R, Ottman R, Maestre G, *et al.* Synergistic effects of traumatic head injury and
44 724 apolipoprotein-epsilon4 in patients with alzheimer's disease. *Neurology* 1995;**45**:555–7.
45 725 doi:10.1212/WNL.45.3.555
- 46 726 35 Silverberg ND, Gardner AJ, Brubacher JR, *et al.* Systematic review of multivariable
47 727 prognostic models for mild traumatic brain injury. *J Neurotrauma* 2015;**32**:517–26.
48 728 doi:10.1089/neu.2014.3600
- 49 729 36 Carroll LJ, Cassidy JD, Peloso PM, *et al.* Prognosis for mild traumatic brain injury: Results of
50 730 the WHO Collaborating Centre Task Force on mild traumatic brain injury. *J Rehabil Med*
51 731 2004;**36**:84–105. doi:10.1080/16501960410023859
- 52 732 37 Hou R, Moss-Morris R, Peveler R, *et al.* When a minor head injury results in enduring
53 733 symptoms: A prospective investigation of risk factors for postconcussional syndrome after
54 734 mild traumatic brain injury. *J Neurol Neurosurg Psychiatry* 2011;**83**:217–23.
55 735 doi:10.1136/jnnp-2011-300767
- 56 736 38 Bazarian JJ, Wong T, Harris M, *et al.* Epidemiology and predictors of post-concussive
57 737 syndrome after minor head injury in an emergency population. *Brain Inj* 1999;**13**:173–89.

- 1
2
3 738 doi:10.1080/026990599121692
4 739 39 Lannsjö M, Backheden M, Johansson U, *et al.* Does head CT scan pathology predict outcome
5 740 after mild traumatic brain injury? *Eur J Neurol* 2013;**20**:124–9. doi:10.1111/j.1468-
6 741 1331.2012.03813.x
7 742 40 McLean SA, Kirsch NL, Tan-Schriner CU, *et al.* Health status, not head injury, predicts
8 743 concussion symptoms after minor injury. *Am J Emerg Med* 2009;**27**:182–90.
9 744 doi:10.1016/J.AJEM.2008.01.054
10 745 41 Meares S, Shores EA, Taylor AJ, *et al.* The prospective course of postconcussion syndrome:
11 746 The role of mild traumatic brain injury. *Neuropsychology* 2011;**25**:454–65.
12 747 doi:10.1037/a0022580
13 748 42 Cnossen MC, Winkler EA, Yue JK, *et al.* Development of a Prediction Model for Post-
14 749 Concussive Symptoms following Mild Traumatic Brain Injury: A TRACK-TBI Pilot Study. *J*
15 750 *Neurotrauma* 2017;**34**:2396–409. doi:10.1089/neu.2016.4819
16 751 43 Ponsford J, Willmott C, Rothwell A, *et al.* Factors influencing outcome following mild
17 752 traumatic brain injury in adults. *J Int Neuropsychol Soc* 2000;**6**:568–79.
18 753 doi:10.1017/S1355617700655066
19 754 44 Meares S, Shores EA, Taylor AJ, *et al.* Mild traumatic brain injury does not predict acute
20 755 postconcussion syndrome. *J Neurol Neurosurg Psychiatry* 2008;**79**:300–6.
21 756 doi:10.1136/jnnp.2007.126565
22 757 45 Alexander MP. Neuropsychiatric correlates of persistent postconcussive syndrome. *J Head*
23 758 *Trauma Rehabil* 1992;**7**:60–9. doi:10.1097/00001199-199206000-00009
24 759 46 Kashluba S, Paniak C, Casey JE. Persistent Symptoms Associated with Factors Identified by
25 760 the WHO Task Force on Mild Traumatic Brain Injury. *Clin Neuropsychol* 2008;**22**:195–208.
26 761 doi:10.1080/13854040701263655org/10.1080/13854040701263655
27 762 47 Ponsford J, Cameron P, Fitzgerald M, *et al.* Predictors of postconcussive symptoms 3 months
28 763 after mild traumatic brain injury. *Neuropsychology* 2012;**26**:304–13. doi:10.1037/a0027888
29 764 48 Ponsford J, Nguyen S, Downing M, *et al.* Factors associated with persistent post-concussion
30 765 symptoms following mild traumatic brain injury in adults. *J Rehabil Med* 2019;**51**:32–9.
31 766 doi:10.2340/16501977-2492
32 767 49 Thornhill S, Teasdale GM, Murray GD, *et al.* Disability in young people and adults one year
33 768 after head injury: prospective cohort study. *BMJ* 2000;**320**:1631–5.
34 769 doi:10.1136/BMJ.320.7250.1631
35 770 50 Topolovec-Vranic J, Pollmann-Mudryj MA, Ouchterlony D, *et al.* The value of serum
36 771 biomarkers in prediction models of outcome after mild traumatic brain injury. *J Trauma - Inj*
37 772 *Infect Crit Care* 2011;**71**:S478–86. doi:10.1097/TA.0b013e318232fa70
38 773 51 Roy D, Peters ME, Everett A, *et al.* Loss of consciousness and altered mental state predicting
39 774 depressive and post-concussive symptoms after mild traumatic brain injury. *Brain Inj*
40 775 2019;**33**:1064–9. doi:10.1080/02699052.2019.1606447
41 776 52 Ganti L, Khalid H, Patel PS, *et al.* Who gets post-concussion syndrome? An emergency
42 777 department-based prospective analysis. *Int J Emerg Med* 2014;**7**:31. doi:10.1186/s12245-014-
43 778 0031-6
44 779 53 Nelson LD, Furger RE, Ranson J, *et al.* Acute clinical predictors of symptom recovery in
45 780 emergency department patients with uncomplicated mild traumatic brain injury (mTBI) or
46 781 non-TBI injuries. *J Neurotrauma* 2018;**35**:249–59. doi:10.1089/neu.2017.4988
47 782 54 King NS. Emotional, neuropsychological, and organic factors: their use in the prediction of
48 783 persisting postconcussion symptoms after moderate and mild head injuries. *J Neurol*
49 784 *Neurosurg Psychiatry* 1996;**61**:75–81. doi:10.1136/JNNP.61.1.75
50 785 55 Sheedy J, Geffen G, Donnelly J, *et al.* Emergency Department Assessment of Mild Traumatic
51 786 Brain Injury and Prediction of Post-Concussion Symptoms at One Month Post Injury. *J Clin*
52 787 *Exp Neuropsychol* 2006;**28**:755–72. doi:10.1080/13803390591000864
53 788 56 Sheedy J, Harvey E, Faux S, *et al.* Emergency department assessment of mild traumatic brain
54 789 injury and the prediction of postconcussive symptoms: A 3-month prospective study. *J Head*
55 790 *Trauma Rehabil* 2009;**24**:333–43. doi:10.1097/HTR.0b013e3181aea51f
56 791 57 Faux S, Sheedy J, Delaney R, *et al.* Emergency department prediction of post-concussive
57 792 syndrome following mild traumatic brain injury: An international cross-validation study. *Brain*

- 1
2
3 793 *Inj* 2011;**25**:14–22. doi:10.3109/02699052.2010.531686
- 4 794 58 Binder LM, Rohling ML, Larrabee GJ. A review of mild head trauma. part I: Meta-analytic
5 795 review of neuropsychological studies. *J Clin Exp Neuropsychol* 1997;**19**:421–31.
6 796 doi:10.1080/01688639708403870
- 7 797 59 Reitan RM, Wolfson D. Emotional disturbances and their interaction with neuropsychological
8 798 deficits. *Neuropsychol Rev* 1997;**7**:3–19. doi:10.1007/BF02876970
- 9 799 60 Dikmen S, Machamer J, Temkin N. Mild Head Injury: Facts and Artifacts. *J Clin Exp*
10 800 *Neuropsychol* 2001;**23**:729–38. doi:10.1076/jcen.23.6.729.1019
- 11 801 61 Taylor AE, Cox CA, Mailis A. Persistent neuropsychological deficits following whiplash:
12 802 Evidence for chronic mild traumatic brain injury? *Arch Phys Med Rehabil* 1996;**77**:529–35.
13 803 doi:10.1016/S0003-9993(96)90290-7
- 14 804 62 Dash PK, Zhao J, Hergenroeder G, *et al.* Biomarkers for the Diagnosis, Prognosis, and
15 805 Evaluation of Treatment Efficacy for Traumatic Brain Injury. *Neurotherapeutics* 2010;**7**:100–
16 806 14. doi:10.1016/j.nurt.2009.10.019
- 17 807 63 Zetterberg H, Smith DH, Blennow K. Biomarkers of mild traumatic brain injury in
18 808 cerebrospinal fluid and blood. *Nat Rev Neurol* 2013;**9**:201–10. doi:10.1038/nrneurol.2013.9
- 19 809 64 Papa L, Ramia MM, Edwards D, *et al.* Systematic review of clinical studies examining
20 810 biomarkers of brain injury in athletes after sports-related concussion. *J Neurotrauma*.
21 811 2015;**32**:661–73. doi:10.1089/neu.2014.3655
- 22 812 65 Undén J, Ingebrigtsen T, Romner B. Scandinavian guidelines for initial management of
23 813 minimal, mild and moderate head injuries in adults: An evidence and consensus-based update.
24 814 *BMC Med* 2013;**11**:50. doi:10.1186/1741-7015-11-50
- 25 815 66 Bazarian JJ, Biberthaler P, Welch RD, *et al.* Serum GFAP and UCH-L1 for prediction of
26 816 absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study.
27 817 *Lancet Neurol* 2018;**17**:782–9. doi:10.1016/S1474-4422(18)30231-X
- 28 818 67 Meyer J, Bartolomei C, Sauer A, *et al.* The relationship between fluid biomarkers and clinical
29 819 outcomes in sports-related concussions: a systematic review. *Brain Inj* 2020;**1**:1–11.
30 820 doi:10.1080/02699052.2020.1802780
- 31 821 68 Yuh EL, Mukherjee P, Lingsma HF, *et al.* Magnetic resonance imaging improves 3-month
32 822 outcome prediction in mild traumatic brain injury. *Ann Neurol* 2013;**73**:224–35.
33 823 doi:10.1002/ana.23783
- 34 824 69 Karr JE, Iverson GL, Berghem K, *et al.* Complicated mild traumatic brain injury in older
35 825 adults: Post-concussion symptoms and functional outcome at one week post injury. *Brain Inj*
36 826 2020;**34**:26–33. doi:10.1080/02699052.2019.1669825
- 37 827 70 Ryan LM, Warden DL. Post concussion syndrome. *Int Rev Psychiatry* 2003;**15**:310–6.
38 828 doi:10.1080/09540260310001606692
- 39 829 71 Haider MN, Leddy JJ, Wilber CG, *et al.* The Predictive Capacity of the Buffalo Concussion
40 830 Treadmill Test After Sport-Related Concussion in Adolescents. *Front Neurol* 2019;**10**:395.
41 831 doi:10.3389/fneur.2019.00395
- 42 832 72 Whitney SL, Eagle SR, Marchetti G, *et al.* Association of acute vestibular/ocular motor
43 833 screening scores to prolonged recovery in collegiate athletes following sport-related
44 834 concussion. *Brain Inj* 2020;**34**:842–7. doi:10.1080/02699052.2020.1755055
- 45 835 73 Lau BC, Collins MW, Lovell MR. Sensitivity and specificity of subacute computerized
46 836 neurocognitive testing and symptom evaluation in predicting outcomes after sports-related
47 837 concussion. *Am J Sports Med* 2011;**39**:1209–16. doi:10.1177/0363546510392016
- 48 838 74 Sullivan KA, Kempe CB, Edmed SL, *et al.* Resilience and Other Possible Outcomes After
49 839 Mild Traumatic Brain Injury: a Systematic Review. *Neuropsychol. Rev.* 2016;**26**:173–85.
50 840 doi:10.1007/s11065-016-9317-1
- 51 841 75 Anderson JFI, Fitzgerald P. Associations between coping style, illness perceptions and self-
52 842 reported symptoms after mild traumatic brain injury in prospectively studied pre-morbidly
53 843 healthy individuals. *Neuropsychol Rehabil* 2020;**30**:1115–28.
54 844 doi:10.1080/09602011.2018.1556706
- 55 845 76 Kristman VL, Borg J, Godbolt AK, *et al.* Methodological issues and research
56 846 recommendations for prognosis after mild traumatic brain injury: Results of the international
57 847 collaboration on mild traumatic brain injury prognosis. *Arch. Phys. Med. Rehabil.* 2014;**95**.

- 1
2
3 848 doi:10.1016/j.apmr.2013.04.026
4 849 77 Zemek R, Barrowman N, Freedman SB, *et al.* Clinical risk score for persistent postconcussion
5 850 symptoms among children with acute concussion in the ED. *J Am Med Assoc* 2016;**315**:1014–
6 851 25. doi:10.1001/jama.2016.1203
7 852 78 Australian Bureau of Statistics. 2016 Census QuickStats Perth. Aust. Bur. Stat. QuickStats.
8 853 2017. https://quickstats.censusdata.abs.gov.au/census_services/getproduct/census/2016/quickstat/5009?opendocument (accessed 23 Sep 2020).
9 854
10 855 79 Australian Bureau of Statistics. Greater Perth: Region Data Summary. Aust. Bur. Stat.
11 856 2016. https://itt.abs.gov.au/itt/r.jsp?RegionSummary®ion=5GPER&dataset=ABS_REGIONAL_ASGS&geoconcept=REGION&datasetASGS=ABS_REGIONAL_ASGS&datasetLGA=ABS_NRP9_LGA®ionLGA=REGION®ionASGS=REGION (accessed 23 Sep 2020).
12 857
13 858 80 Carroll LJ, Cassidy JD, Holm L, *et al.* Methodological issues and research recommendations
14 859 for mild traumatic brain injury: The WHO Collaborating Centre Task Force on Mild
15 860 Traumatic Brain Injury. *J Rehabil. Med. Suppl.* 2004;:113–25.
16 861
17 862 doi:10.1080/16501960410023877
18 863 81 Theadom A, Barker-Collo S, Feigin VL, *et al.* The spectrum captured: A methodological
19 864 approach to studying incidence and outcomes of traumatic brain injury on a population level.
20 865 *Neuroepidemiology* 2012;**38**:18–29. doi:10.1159/000334746
21 866 82 Lovell MR, Iverson GL, Collins MW, *et al.* Measurement of symptoms following sports-
22 867 related concussion: Reliability and normative data for the post-concussion scale. *Appl*
23 868 *Neuropsychol* 2006;**13**:166–74. doi:10.1207/s15324826an1303_4
24 869 83 Kontos AP, Elbin RJ, Schatz P, *et al.* A revised factor structure for the post-concussion
25 870 symptom scale: Baseline and postconcussion factors. *Am J Sports Med* 2012;**40**:2375–84.
26 871
27 872 doi:10.1177/0363546512455400
28 873 84 Von Steinbüchel N, Wilson L, Gibbons H, *et al.* Quality of life after brain injury (QOLIBRI):
29 874 Scale development and metric properties. *J Neurotrauma* 2010;**27**:1167–85.
30 875
31 876 doi:10.1089/neu.2009.1076
32 877 85 Rapp PE, Keyser DO, Albano A, *et al.* Traumatic brain injury detection using
33 878 electrophysiological methods. *Front Hum Neurosci* 2015;**9**:11. doi:10.3389/fnhum.2015.00011
34 879 86 Thatcher RW, North DM, Curtin RT, *et al.* An EEG severity index of traumatic brain injury. *J*
35 880 *Neuropsychiatry Clin Neurosci* 2001;**13**:77–87. doi:10.1176/jnp.13.1.77
36 881 87 Randolph C. *Repeatable Battery for the Assessment of Neuropsychological Status: Update.*
37 882 Bloomington, MN: USA: : PsychCorp 2012.
38 883 88 Lezak M, Howieson D, Loring D, *et al.* *Neuropsychological Assessment.* 4th ed. New York: :
39 884 Oxford University Press 2004.
40 885 89 Rey A. *L'examen clinique en psychologie.* Paris: : Presses Universitaires de France 1964.
41 886 90 Lovibond SH, Lovibond PF. *Manual for the Depression and Anxiety Stress Scales.* 2nd ed.
42 887 Sydney, NSW: : Psychology Foundation 1995.
43 888 91 Derogatis L. *BSI 18 Brief Symptom Inventory 18.* Bloomington, MN: USA: : Pearson Clinical
44 889 2001.
45 890 92 Smith BW, Dalen J, Wiggins K, *et al.* The Brief Resilience Scale: Assessing the Ability to
46 891 Bounce Back. *Int J Behav Med* 2008;**15**:194–200. doi:10.1080/10705500802222972
47 892 93 Turner H, Bryant-Waugh R, Peveler R, *et al.* A Psychometric Evaluation of an English
48 893 Version of the Utrecht Coping List. *Eur Eat Disord Rev* 2012;**20**:339–42.
49 894
50 895 doi:10.1002/erv.2173
51 896 94 Schreurs PJG, Van de Willige G, Brosschot JF, *et al.* *De Utrechtse Coping Lijst. Herziene*
52 897 *Handleiding (revised manual).* Lisse, The Netherlands: : Swets en Zeitlinger 1993.
53 898 95 Haider MN, Johnson SL, Mannix R, *et al.* The Buffalo Concussion Bike Test for Concussion
54 899 Assessment in Adolescents. *Sports Health* 2019;**11**:492–7. doi:10.1177/1941738119870189
55 900 96 Warburton DER, Jamnik VK, Bredin SSD, *et al.* Evidence-based risk assessment and
56 901 recommendations for physical activity clearance: an introduction 1 This paper is one of a
57 902 selection of papers published in this Special Issue, entitled Evidence-based risk assessment and
58 903 recommendations for physical activity clearance, and has undergone the Journal's usual peer
59 904 review process. . *Appl Physiol Nutr Metab* 2011;**36**:S1–2. doi:10.1139/h11-060
60 905 97 Scherr J, Wolfarth B, Christle JW, *et al.* Associations between Borg's rating of perceived

- 1
2
3 903 exertion and physiological measures of exercise intensity. *Eur J Appl Physiol* 2013;**113**:147–
4 904 55. doi:10.1007/s00421-012-2421-x
- 5 905 98 Mucha A, Collins MW, Elbin RJ, *et al.* A brief vestibular/ocular motor screening (VOMS)
6 906 assessment to evaluate concussions: Preliminary findings. *Am J Sports Med* 2014;**42**:2479–86.
7 907 doi:10.1177/0363546514543775
- 8 908 99 Gorgolewski K, Burns CD, Madison C, *et al.* Nipype: A Flexible, Lightweight and Extensible
9 909 Neuroimaging Data Processing Framework in Python. *Front Neuroinform* 2011;**5**:13.
10 910 doi:10.3389/fninf.2011.00013
- 11 911 100 Kluyver T, Ragan-Kelley B, Pérez F, *et al.* Jupyter Notebooks—a publishing format for
12 912 reproducible computational workflows. In: Loizides F, Schmidt B, eds. *Positioning and Power*
13 913 *in Academic Publishing: Players, Agents and Agendas - Proceedings of the 20th International*
14 914 *Conference on Electronic Publishing, ELPUB 2016*. Amsterdam, The Netherlands: : IOS Press
15 915 2016. 87–90. doi:10.3233/978-1-61499-649-1-87
- 16 916 101 Gorgolewski KJ, Auer T, Calhoun VD, *et al.* The brain imaging data structure, a format for
17 917 organizing and describing outputs of neuroimaging experiments. *Sci Data* 2016;**3**:1–9.
18 918 doi:10.1038/sdata.2016.44
- 19 919 102 Smith SM, Jenkinson M, Johansen-Berg H, *et al.* Tract-based spatial statistics: Voxelwise
20 920 analysis of multi-subject diffusion data. *Neuroimage* 2006;**31**:1487–505.
21 921 doi:10.1016/J.NEUROIMAGE.2006.02.024
- 22 922 103 Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)-A metadata-
23 923 driven methodology and workflow process for providing translational research informatics
24 924 support. *J Biomed Inform* 2009;**42**:377–81. doi:10.1016/j.jbi.2008.08.010
- 25 925 104 Harris PA, Taylor R, Minor BL, *et al.* The REDCap consortium: Building an international
26 926 community of software platform partners. *J. Biomed. Inform.* 2019;**95**:103208.
27 927 doi:10.1016/j.jbi.2019.103208
- 28 928 105 Alla S, John Sullivan S, McCrory P. Defining asymptomatic status following sports
29 929 concussion: Fact or fallacy? *Br. J. Sports Med.* 2012;**46**:562–9. doi:10.1136/bjsm.2010.081299
30 930
31 931
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

932 Author Affiliations

- 933 ¹ Curtin Health Innovation Research Institute, Curtin University, Bentley, WA 6102, Australia
- 934 ² Perron Institute for Neurological and Translational Science, Nedlands, WA 6009, Australia
- 935 ³ Curtin School of Population Health, Curtin University, Bentley, WA 6102, Australia
- 936 ⁴ School of Surgery, The University of Western Australia, Crawley, WA 6009, Australia
- 937 ⁵ School of Psychological Science, The University of Western Australia, Crawley, WA 6009,
938 Australia
- 939 ⁶ Discipline of Exercise Science, Murdoch University, Murdoch, WA 6150, Australia
- 940 ⁷ Australian Alzheimer's Research Foundation, Nedlands, WA 6009, Australia
- 941 ⁸ School of Human Sciences, The University of Western Australia, Crawley, WA 6009, Australia
- 942 ⁹ Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, WA 6150,
943 Australia.
- 944 ¹⁰ School of Physiotherapy and Exercise Science, Curtin University, Bentley, WA 6102, Australia
- 945 ¹¹ Emergency Department, Fiona Stanley Hospital, Murdoch, WA 6150, Australia
- 946 ¹² Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research,
947 Nedlands, WA 6009, Australia
- 948 ¹³ Emergency Department, Rockingham General Hospital, Cooloongup, WA 6168, Australia
- 949 ¹⁴ Emergency Department, Joondalup Health Campus, Joondalup, WA 6027, Australia
- 950 ¹⁵ Emergency Department, Saint John of God Midland Public Hospital, Midland, WA 6056, Australia
- 951 ¹⁶ School of Medicine, The University of Notre Dame, Fremantle, WA 6959, Australia
- 952 ¹⁷ Curtin Medical School, Curtin University, Bentley, WA 6102, Australia
- 953 ¹⁸ Emergency Department, Saint John of God Murdoch Private Hospital, Murdoch, WA 6150,
954 Australia
- 955 ¹⁹ Emergency Department, Royal Perth Hospital, Perth, WA 6000, Australia
- 956 ²⁰ Royal Flying Doctor Service- Western Operations, Jandakot, WA 6164, Australia
- 957 ²¹ Emergency Department, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia
- 958 ²² Division of Emergency Medicine, School of Medicine, The University of Western Australia,
959 Crawley, WA 6009, Australia
- 960 ²³ Emergency Department, Armadale Health Service, Mount Nasura, WA 6112, Australia
- 961 ²⁴ Statewide Director of Neurosurgery Western Australia, Department of Health, Perth, WA 6000,
962 Australia
- 963 ²⁵ Head of Department, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia
- 964 ²⁶ Head of Department, Royal Perth Hospital, Perth, WA 6000, Australia
- 965 ²⁷ Head of Department, Fiona Stanley Hospital, Murdoch, WA 6150, Australia
- 966 ²⁸ Telethon Kids Institute, West Perth, WA 6005, Australia
- 967 ²⁹ Neurological Intervention and Imaging Service of Western Australia, Sir Charles Gairdner
968 Hospital, Nedlands, WA 6009, Western Australia

1
2
3 969 ³⁰ Emergency Medicine, Royal Perth Hospital, The University of Western Australia, Perth 6000,
4 Australia

5 970
6 971 ³¹ Department of Medical Education & General Practice, The First Affiliated Hospital, Sun Yat-Sen
7 University, Guangzhou, China
8 972

9 973

10 974

11 974
12 975 **Authors' contributions** MF DF CP MB ML SR DX conceptualised the study and participated in initial
13 study design, with assistance from AG JT ET FB AvH. AG, SCH, JT, FB and MF drafted the manuscript.
14 976 AG prepared visual content and coordinated manuscript revisions. MF DF CP MB ML SR DX obtained
15 977 the research funding. All other authors (ET SM AR GA BS SvS PB JI AC AM DX SR SH GC ML MB
16 978 CP DF) contributed to study design and revisions of the manuscript.
17 979
18 980

19 980

20 980
21 981 **Funding** The funding for this research project was provided by the Neurotrauma Research Program
22 WA (NRP), and was funded by the State Government of Western Australia through the Department of
23 982 Health. We wish to thank the Perron Institute for Neurological and Translational Science for its support
24 983 for this research through the award of a Perron Internal Grant.
25 984
26 985

27 985

28 985
29 986 **Competing Interests** Melinda Fitzgerald is the Chief Executive Officer of the charitable organization
30 *Vision TBI (Ltd.)*, trading as *Connectivity - Traumatic Brain Injury Australia*. AG acknowledges the
31 987 Perron Institute for Neurological and Translational Sciences for PhD stipend support.
32 988
33 989

34 989

35 990 **Patient consent for publication** Not required.
36 991

37 991

38 991
39 992 **Ethics Approval** This study protocol has been approved by the Human Research Ethics committees of
40 993 Royal Perth Hospital (#RGS0000003024), Curtin University (HRE2019-0209), Ramsay Health Care
41 994 (#2009), and St John of God Health Care (#1628).
42 995

43 995

44 996 **Provenance and peer review** Not commissioned; externally peer reviewed
45 997

46 997
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 998 **Figure Legends**
4
5 999

6 1000 *Figure 1.* Map showing location of hospital emergency departments (red crosses) throughout the Greater Perth Area from
7 1001 which prospective *CREST* participants are recruited, relative to the location of the *CREST* Research Hub (blue diamond). *Note:*
8 1002 SJOG: Saint John of God Hospital
9 1003

10 1004
11 1005 *Figure 2.* Flow diagram of the *CREST* study design. Participants are recruited via Hospital ED or Community-Based Pathways
12 1006 using a dedicated *Participant Referral Form*. Following the receipt of a completed *Participant Referral Form*, either by email
13 1007 or fax, a member of the *CREST* research team uses a dedicated mobile telephone number to contact prospective participants.
14 1008 During this phone call, interested participants are briefed on the study aims and procedures, and verbal consent is obtained to
15 1009 participate in the study. Following this, the *Phase I* semi-structured telephone interview is conducted and upon its conclusion
16 1010 participants are asked if they also wish to participate in *Phase II* of the study. If interested, the *CREST* research team member
17 1011 completes a telephone screen to assess the participant's eligibility to undertake the additional components of *Phase II*. If a
18 1012 participant is deemed eligible, a testing session is organised at the *CREST* Research Hub. Both *Phase I* and *Phase II*
19 1013 components are conducted within 7 days of a participant sustaining an mTBI. All participants are followed-up by telephone
20 1014 interview at 1-, 3-, 6- and 12-months following the date of injury. *Note:* * Comprises the Curtin University and Perron Institute
21 1015 for Neurological and Translational Science tenancies, which are located at Queen Elizabeth II Medical Centre, Nedlands (Perth,
22 1016 Western Australia); †: MRI may be conducted up to 9 days following participant's mTBI; ‡: Quality of Life is assessed using
23 1017 the QOLIBRI-OS at 3-, 6- and 12-month follow-ups only. Abbreviations: EDs: Emergency departments; GPs: General
24 1018 practitioners; MRI: Magnetic resonance imaging; mTBI: mild traumatic brain injury; NPA: Neuropsychological assessment;
25 1019 qEEG: Quantitative electroencephalography; VOMS: Vestibular/Ocular Motor Screening test; WA: Western Australia.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

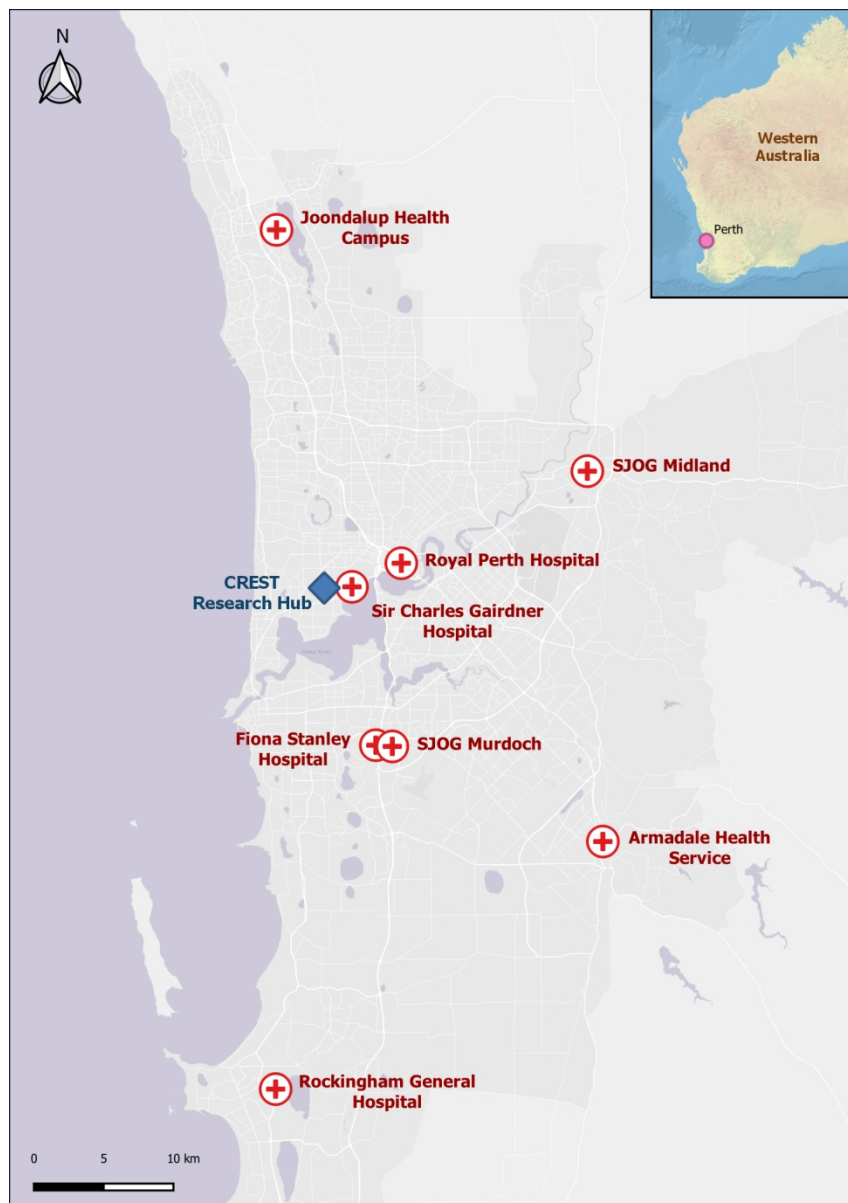


Figure 1. Map showing location of hospital emergency departments (red crosses) throughout the Greater Perth Area from which prospective CREST participants are recruited, relative to the location of the CREST Research Hub (blue diamond). Note: SJOG: Saint John of God Hospital

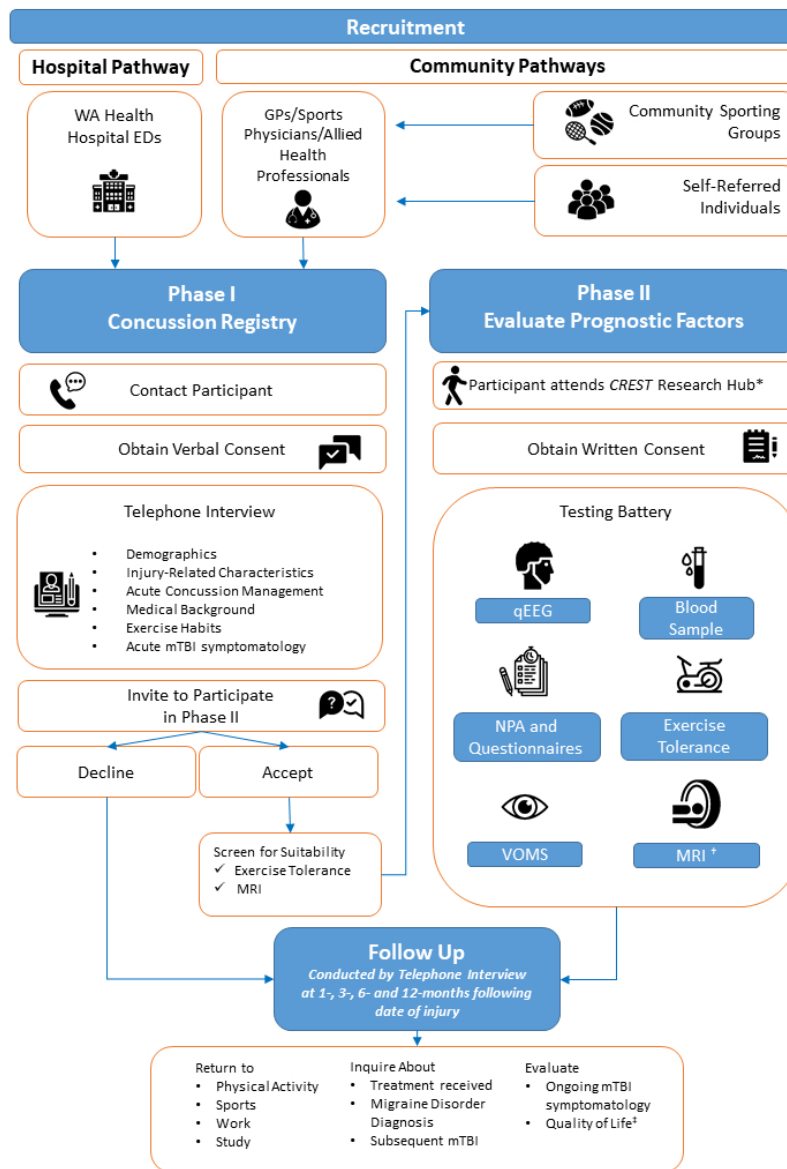


Figure 2. Flow diagram of the CREST study design. Participants are recruited via Hospital ED or Community-Based Pathways using a dedicated Participant Referral Form. Following the receipt of a completed Participant Referral Form, either by email or fax, a member of the CREST research team uses a dedicated 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

1
2
3 of Life is assessed using the QOLIBRI-OS at 3-, 6- and 12-month follow-ups only. Abbreviations: EDs:
4 Emergency departments; GPs: General practitioners; MRI: Magnetic resonance imaging; mTBI: mild
5 traumatic brain injury; NPA: Neuropsychological assessment; qEEG: Quantitative electroencephalography;
6 VOMS: Vestibular/Ocular Motor Screening test; WA: Western Australia.

7 190x275mm (96 x 96 DPI)

1
2
3 **Predicting Outcome Following Mild Traumatic Brain Injury: Protocol for the**
4 **Longitudinal, Prospective, Observational Concussion Recovery**
5 **(CREST) Cohort Study**
6
7
8
9

10
11 **Gozt, AK et al.**
12
13

14
15
16 **Supplementary information**
17
18

- 19
20 1. Document 1. Participant site referral form.
21 2. Figure 1. The 10-20 International system of EEG electrode placement.
22 3. Table 1. MRI scan parameters.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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, foginess) that may or may not be transient?

Please forward the completed form to:

concussionstudy@curtin.edu.au

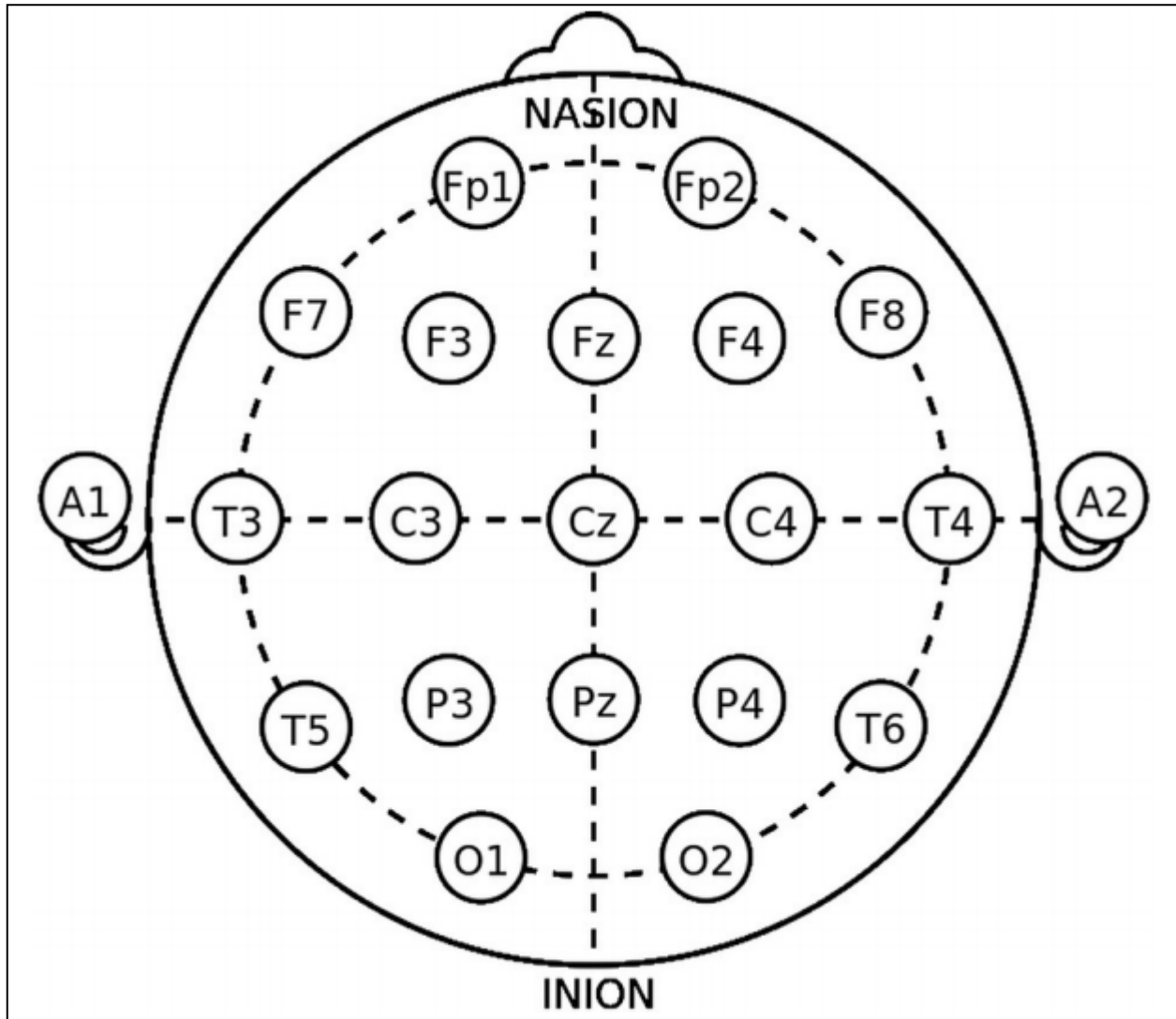
or

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 (#RGS000003024) 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.

<i>Sequence</i>	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 3	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 $\Delta 7.7$	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/mm²) [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