

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The CONcussion in non-aThletes; Assessment of CogniTion and Symptomatology (CONTACTS) study protocol: An exploratory cohort study investigating the utility of sports concussion assessment tools and salivary micro-RNAs to diagnose concussion in NHS patients
<b>AUTHORS</b>	Toman, Emma; Riley, Max; Hodgson, Sam; Yakoub, Kamal; Cooper, Lauren; Bishop, Jon; Naumann, David; Welbury, Richard; Hammond, Douglas; Di Pietro, Valentina; Belli, Antonio

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Indira Devi, Bhagavatula National Institute of Mental Health and Neuro Sciences
<b>REVIEW RETURNED</b>	11-May-2022

<b>GENERAL COMMENTS</b>	Concussion is an important aspect of road traffic accidents . unrecognized / inadequately managed concussion has long term effects in return to work/society and quality of life . microrna testing of saliva in suspected concussion( if sensitive )is useful.
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<b>REVIEWER</b>	Patricios, Jon Wits Sport and Health (WiSH)
<b>REVIEW RETURNED</b>	09-Jun-2022

<b>GENERAL COMMENTS</b>	<p>General comments</p> <p>This is an interesting protocol and study that seeks to translate findings from a sporting environment into a clinical setting (usually it is the other way around)</p> <p>The references study was published in a high impact journal and has received widespread publicity.</p> <p>The identification of mTBI in the ED is often overlooked, making the study relevant.</p> <p>Specific comments</p> <p>The rugby mRNA study should be referenced in the opening paragraph.</p> <p>The “Strengths and Limitations” section should be sub-divided into strengths and limitations</p> <p>“Inclusion of older patients and those with mental health conditions or concurrent intoxication.” Is this meant as limitation? Please elaborate.</p>
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	<p>“Those with premorbid neurological or cognitive issues were unable to be included in this Study.” This is neither a strength nor a limitation but an exclusion criterion.</p> <p>P6L33 “It also demonstrates great promise for use in non-athletes in the detection of concussion in the ED.” This is presumptive. The tests(s) have not yet demonstrated promise. I would rephrase to read “The test potentially may be of use in the ED....”</p> <p>P6L55 “synthesis of current research, public input and expert panel review...” Should read “...systematic review of recent research and expert panel input...”</p> <p>P10L26 Under Study Design  “Patients of interest include adult patients who require hospital admission following non-sporting isolated maxillofacial trauma. Recruiting patients with maxillofacial trauma to the concussion arm ensures that there is objective evidence of head injury having occurred” should be corrected to read “...Patients of interest are...”</p> <p>Inclusion Criteria  P11L33 Will all included patients receive brain imaging?  P12L11 “Patients with isolated limb injury are a suitable control group because they have a comparable burden of injury and will receive similar management to the concussed group such as operative interventions and pain management.” This statement doesn’t seem appropriate. How does a single limb injury ) e.g., ankle ligament tears” have a “similar burden of injury”? Also, most limb injuries will not require surgery. Consider rephrasing. Would it not be more appropriate to use “upper limb injuries requiring surgery.”</p> <p>Screening  P15L26 This is the first time the ACRM definition of mTBI is mentioned; consider bringing this in to the introduction and clarify whether both the CISG and the ACRM definitions need to be satisfied or just one.  P15L39 should read “If the data have been analysed...”</p> <p>P17L17 What controls are in place to ensure that the ImpACT test is performed by the patient and under the correct conditions?  P17L56 Perhaps explain the exact technique of taking the saliva specimen (e.g., check swab)</p>
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<b>REVIEWER</b>	Sicard , Veronik Mind Research Network
<b>REVIEW RETURNED</b>	23-Jun-2022

<b>GENERAL COMMENTS</b>	<p>Abstract  Page 3, line 19 and in the Introduction. Please define NHS patients for those not in the UK  Page 3, line 45. It is not clear from the Abstract that you will be doing some of the assessments in the hospitals, then some remotely, and also a phone interview.</p> <p>Introduction  Page 5, line 19. While the definition is long, many would argue it is not clear and many researchers in the field do not agree with the definition. I would suggest rewording this sentence</p>
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	<p>Page 6, lines 24-26. What is 'successfully identified' in terms of sensitivity and specificity (or diagnostic accuracy)? Can you provide more context on these results?</p> <p>Page 6, line 53. This sentence reads weird: The SCAT5 is validated for assessment ... Also, this could be debated. Authors should provide more rationale around the 'validated' statement. The SCAT5 has been shown to be sensitive to concussion immediately after the injury but does not retain its sensitivity over time. This nuance should be clear.</p> <p>Page 7, ImPACT section. The authors use 'ImPACT tool', 'ImPACT tools', 'the test', 'ImPACT assessment', 'ImPACT test' across the section to refer to the same thing. It should be 'The ImPACT' throughout the section.</p> <p>Page 7, ImPACT section. There should be a description of the different tests included in the test battery and how the 5 composite scores are computed.</p> <p><b>Rationale</b></p> <p>Page 9, lines 13. 'mTBI' – Do the authors consider concussions and mTBI synonymously? If so, this should be made clear in the first paragraph of the introduction.</p> <p>Page 9, first paragraph. There is a lot of repetition in the paragraph. Can the authors make it more concise?</p> <p>Page 9, Rationale in general. In the rationale, the authors indicate that 'a longer-term qualitative review of the tool would add depth to existing data' and 'more innovative ways of monitoring recovery and symptoms in such patients need to be developed ideally remotely', however, Introduction does not present these concepts at all. I would recommend the authors work on the Introduction to introduce these concepts rather than focusing only on the diagnosis.</p> <p>Goals. I would add a Goals section to make it clearer to the readers. It was not clear from the start what the project would be about. Especially because it did not match the aims in the Abstract.</p> <p><b>Methods and Analysis</b></p> <p>Page 10, lines 28. The rationale for including only participants with a concussion AND an isolated maxillofacial trauma is unclear. Would the maxillofacial trauma result in symptoms akin to a concussion or at the very least contribute to concussion symptoms? How will the authors delineate what is due to the concussion and what is due to the maxillofacial trauma? This will be a major limitation of the study since most concussion studies did not have such an inclusion criterion.</p> <p>Page 10, Eligibility Criteria. By deciding to include only patients requiring admission, the authors might exclude the 'milder' cases of concussions, therefore their sample might not represent most concussions. While I believe this is okay to increase the rate of follow-up during this COVID time, this should be added to the limitations on page 4.</p> <p>Page 12, lines 9. Who are 'Patients of interest'? All the patients? Or a subset?</p> <p>Page 14, line 50. 'Wherever possible, informed consent will be obtained from the patient, however due to the nature of concussion, this may not be possible'. Will only patients with concussions/mild TBI be included in the study?</p> <p><b>Overall comments</b></p>
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	<p>Overall, I would suggest the authors carefully review their manuscript and remove wordiness to improve clarity and conciseness. Tools such as Grammarly or Antidote may be helpful. The APA guide is also a great resource. Here are some examples:</p> <ul style="list-style-type: none"> <li>- Page 7, line 3: vast majority → most</li> <li>- Page 7, lines 26-27: widely used across a variety of professional sports → widely used in professional sports</li> <li>- Page 19, lines 10-15: The phase 1 data will also help inform the selection of the most appropriate primary outcome measure for the main study and provide data to facilitate estimation of the sample size required for the main study → Phase 1 data will inform the selection of the primary outcomes for the main study and provide estimates for sample size calculations.</li> </ul>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Prof. Bhagavatula Indira Devi, National Institute of Mental Health and Neuro Sciences

Comments to the Author:

Concussion is an important aspect of road traffic accidents .

unrecognised / inadequately managed concussion has long term effects in return to work/society and quality of life .

microrna testing of saliva in suspected concussion( if sensitive )is useful.

Reviewer: 2

Dr. Jon Patricios, Wits Sport and Health (WiSH)

Comments to the Author:

General comments

This is an interesting protocol and study that seeks to translate findings from a sporting environment into a clinical setting (usually it is the other way around)

The reference study was published in a high impact journal and has received widespread publicity.

The identification of mTBI in the ED is often overlooked, making the study relevant.

Specific comments

The rugby mRNA study should be referenced in the opening paragraph.

The SCRUM study is mentioned in the abstract and subsequently in the first section following introduction to concussion as a whole. We have therefore not changed the location of where SCRUM is mentioned in the manuscript as we feel it more appropriate to lay down the basics of the disease before introducing research.

The “Strengths and Limitations” section should be sub-divided into strengths and limitations

The subdivision of strengths/limitations is not suggested as part of the author guidelines for BMJ Open and so we have not introduced sub-divisions of strengths and limitations section although we have altered some of the content as suggested (see below).

“Inclusion of older patients and those with mental health conditions or concurrent intoxication.” Is this meant as limitation? Please elaborate.

This is a strength as this will improve the clinical translation of any findings. We have elaborated on this point to improve clarity.

“Those with premorbid neurological or cognitive issues were unable to be included in this Study.” This is neither a strength nor a limitation but an exclusion criterion.

It is a limitation- we have expanded on this point also to clarify

P6L33 “It also demonstrates great promise for use in non-athletes in the detection of concussion in the ED.” This is presumptive. The tests(s) have not yet demonstrated promise. I would rephrase to read “The test potentially may be of use in the ED....”

Agree- we have amended the phrasing

P6L55 “synthesis of current research, public input and expert panel review...” Should read “...systematic review of recent research and expert panel input...”

Agree- this has been amended

P10L26 Under Study Design “Patients of interest include adult patients who require hospital admission following non-sporting isolated maxillofacial trauma. Recruiting patients with maxillofacial trauma to the concussion arm ensures that there is objective evidence of head injury having occurred” should be corrected to read “...Patients of interest are...”

Amended

#### Inclusion Criteria

P11L33 Will all included patients receive brain imaging?

No- we have added a sentence to justify the reason for this (NICE guidelines and reflecting current clinical practice)

P12L11 “Patients with isolated limb injury are a suitable control group because they have a comparable burden of injury and will receive similar management to the concussed group such as operative interventions and pain management.” This statement doesn’t seem appropriate. How does a single limb injury ) e.g., ankle ligament tears” have a “similar burden of injury”? Also, most limb injuries will not require surgery. Consider rephrasing.

We have amended the “comparable burden of injury” phrase to include comments about comparable AIS severity codes. Most lower limb injuries that require admission do require surgery compared to those who are discharged- we have reiterated that eligibility requires admission.

Would it not be more appropriate to use “upper limb injuries requiring surgery.”

This point should be clarified by the changes we have made above.

#### Screening

P15L26 This is the first time the ACRM definition of mTBI is mentioned; consider bringing this in to the introduction and clarify whether both the CISG and the ACRM definitions need to be satisfied or just one.

ACRM definition has been added to figure 1 along with the CISG definition so ACRM definition is included in the introduction. Both definitions need to be satisfied- this is reflected in the inclusion criteria.

P15L39 should read “If the data have been analysed...”

Amended

P17L17 What controls are in place to ensure that the ImPACT test is performed by the patient and under the correct conditions?

There are no specific controls as this is a relatively pragmatic study. If the ImPACT cannot be successfully delivered within these realistic conditions then it is cannot be successfully translated into clinical practice. We have included a section in the “baseline and study assessment data” to clarify this.

P17L56 Perhaps explain the exact technique of taking the saliva specimen (e.g., check swab)

We have included the specific technique for saliva sample collection.

Reviewer: 3

Veronik Sicard , Mind Research Network

Comments to the Author:

Abstract

Page 3, line 19 and in the Introduction. Please define NHS patients for those not in the UK

Done

Page 3, line 45. It is not clear from the Abstract that you will be doing some of the assessments in the hospitals, then some remotely, and also a phone interview.

We have added this into the abstract to clarify

Introduction

Page 5, line 19. While the definition is long, many would argue it is not clear and many researchers in the field do not agree with the definition. I would suggest rewording this sentence

Whilst many may not agree with the definition, it is the formal consensus definition and so we have not altered this sentence.

Page 6, lines 24-26. What is 'successfully identified' in terms of sensitivity and specificity (or diagnostic accuracy)? Can you provide more context on these results?

We have added the AUC values for the study in this paragraph

Page 6, line 53. This sentence reads weird: The SCAT5 is validated for assessment ... Also, this could be debated. Authors should provide more rationale around the 'validated' statement. The SCAT5 has been shown to be sensitive to concussion immediately after the injury but does not retain its sensitivity over time. This nuance should be clear.

Agree, the validity is more detailed than we have stated here. We have changed the wording of this paragraph and have added the limitations of its use outside of diagnosis within the first 5 days.

Page 7, ImPACT section. The authors use 'ImPACT tool', 'ImPACT tools', 'the test', 'ImPACT assessment', 'ImPACT test' across the section to refer to the same thing. It should be 'The ImPACT' throughout the section.

Changed

Page 7, ImPACT section. There should be a description of the different tests included in the test battery and how the 5 composite scores are computed.

We have expanded on this significantly

Rationale

Page 9, lines 13. 'mTBI' – Do the authors consider concussions and mTBI synonymously? If so, this should be made clear in the first paragraph of the introduction.

We do consider them synonymous but to avoid confusion we have removed mTBI from the text

Page 9, first paragraph. There is a lot of repetition in the paragraph. Can the authors make it more concise?

We have tightened this paragraph up

Page 9, Rationale in general. In the rationale, the authors indicate that 'a longer-term qualitative review of the tool would add depth to existing data' and 'more innovative ways of monitoring recovery and symptoms in such patients need to be developed ideally remotely', however, Introduction does not present these concepts at all. I would recommend the authors work on the Introduction to introduce these concepts rather than focusing only on the diagnosis.

We have added a section introducing these concepts earlier on in the introduction

Goals. I would add a Goals section to make it clearer to the readers. It was not clear from the start what the project would be about. Especially because it did not match the aims in the Abstract.

We feel the changes we have made thanks to the reviewers comments have already clarified this point and so have not added in an extra goals section

Methods and Analysis

Page 10, lines 28. The rationale for including only participants with a concussion AND an isolated maxillofacial trauma is unclear. Would the maxillofacial trauma result in symptoms akin to a concussion or at the very least contribute to concussion symptoms? How will the authors delineate what is due to the concussion and what is due to the maxillofacial trauma? This will be a major limitation of the study since most concussion studies did not have such an inclusion criterion. We have added an extra sentence here to clarify. We explain in the manuscript that concussion will be diagnosed according to the CISC and ACRM criteria and so we have not expanded on that in this particular section.

OMFS injuries would contribute to some symptoms of concussion (pain, headache, visual issues) but would not fulfil CISC or ACRM definitions without a concussive injury also. We therefore do not believe this is a limitation.

Page 10, Eligibility Criteria. By deciding to include only patients requiring admission, the authors might exclude the 'milder' cases of concussions, therefore their sample might not represent most concussions. While I believe this is okay to increase the rate of follow-up during this COVID time, this should be added to the limitations on page 4.

We have added the non-admitted patients to our limitations section. However, concussion is no longer classified by severity and so "milder cases" do not exist.

Page 12, lines 9. Who are 'Patients of interest'? All the patients? Or a subset?

Clarified

Page 14, line 50. 'Wherever possible, informed consent will be obtained from the patient, however due to the nature of concussion, this may not be possible'. Will only patients with concussions/mild TBI be included in the study?

Correct. This includes patients who are not able to provide valid consent however as concussed patients can still suffer post-traumatic amnesia for up to 24 hours and so may remain confused in ED, at the point where consent is gained.

#### Overall comments

Overall, I would suggest the authors carefully review their manuscript and remove wordiness to improve clarity and conciseness. Tools such as Grammarly or Antidote may be helpful. The APA guide is also a great resource. Here are some examples:

- Page 7, line 3: vast majority → most
- Page 7, lines 26-27: widely used across a variety of professional sports → widely used in professional sports
- Page 19, lines 10-15: The phase 1 data will also help inform the selection of the most appropriate primary outcome measure for the main study and provide data to facilitate estimation of the sample size required for the main study → Phase 1 data will inform the selection of the primary outcomes for the main study and provide estimates for sample size calculations.