**ABSTRACT**

**Introduction** Concussion is a complex pathophysiological process with a wide range of non-specific signs and symptoms. There are currently no objective diagnostic tests to identify concussion, and diagnosis relies solely on history and examination. Recent research has identified a unique panel of microRNAs (miRNAs) that distinguish between concussed and non-concussed rugby players. This study aims to assess the diagnostic utility of salivary miRNAs in concussion for a sample of UK National Health Service patients and whether well-established sports-related concussion (SRC) assessment tools may be translated into the emergency department (ED).

**Methods and analysis** Concussion in Non-athletes: Assessment of Cognition and Symptomatology is a single-centre, prospective, two-phase cohort study. The concussed cohort will consist of participants with maxillofacial trauma and concurrent concussion. The control cohort will consist of participants with isolated limb trauma and no evidence of concussion. Participants will be recruited in the ED and saliva samples will be taken to identify the presence of miRNAs. The SRC assessments being investigated include the Sports Concussion Assessment Test, Fifth Edition (SCAT5), the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) and the ImPACT Quick. Follow-up will be at 24–48 hours in-hospital and remotely via telephone and email at 14 days and 6 months.

**Ethics and dissemination** Ethical approval was granted in February 2021 by the West Midlands Coventry & Warwickshire Research Ethics Committee (ref 20/WM/0299). The investigators intend to submit their study findings for publication in peer-reviewed journals and to disseminate study findings via presentation at academic meetings. The results will also form part of a doctorate thesis, registered at the University of Birmingham.

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

- Incorporated feasibility phase to ensure the study is correctly powered.
- Pragmatic design that allows assessment of potential clinical utility.
- Traditionally excluded groups (older patients and those suffering from mental health conditions and concurrent intoxication) are to be included, to improve the translation into clinical practice.
- COVID-19 may limit the amount of time patients are in the emergency department, and so the design may need to be adapted.
- Those with premorbid neurological or cognitive issues were unable to be included in this study, which may limit the translation of any findings into clinical practice.

**INTRODUCTION**

**Background and previous literature**

Concussion is defined as ‘a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces’.

Signs and symptoms are non-specific and are largely categorised into physical, cognitive, behavioural and sleep. The Concussion in Sport Group (CISG) and the American Congress of Rehabilitation Medicine (ACRM) provide clear definitions of concussion and mild traumatic brain injury (mTBI) with clinical criteria that are summarised in figure 1.

Each year, 1.4 million people present to the emergency department (ED) in England and
Wales with traumatic brain injury (TBI). Since 90% of TBI cases are classified as mild in severity and have an estimated lifetime cost of $5299, concussion represents an extensive financial burden and is a substantial public health concern.

Diagnosis remains the main stumbling block in the management of concussion. There is currently no objective diagnostic test in clinical practice to identify the condition, and therefore, diagnosis relies solely on history and examination. This poses difficulty where there are no witnesses to the event or the patient suffers from existing cognitive, neurological or psychiatric disorders. The CISG has suggested that no single investigation should be used to diagnose concussion. Instead, several techniques should be used in combination with clinical judgement. Two such widely accepted tools include the paper-based Sports Concussion Assessment Tool, Fifth Edition (SCAT5) and the computerised neurocognitive Immediate Post-Concussion Assessment and Cognitive Testing (ImpACT). Combined, these tools assess a wide variety of domains that can be affected by concussion including physical signs, symptoms, memory, concentration, balance, gait, reaction time and attention.

Selection bias is the most common drawback of applying existing evidence to non-athletes. Older people, those under the influence of alcohol or drugs, and patients with existing cognitive, neurological or psychiatric conditions have traditionally been excluded from previous studies. This means that any prior findings may not apply to the overall UK National Health Service (NHS) population presenting to services with concussion.

In addition to diagnosis, the follow-up of concussed patients within the NHS needs to be addressed. The main difficulty in following up such individuals is the sheer number of patients suffering concussions. This would make face-to-face clinic follow-up of all patients a huge logistical challenge and costly to an already cash-strapped NHS. Innovative methods of follow-up should be researched and would likely involve remote reviews, as have become more common since the COVID-19 pandemic.

Salivary microRNAs (miRNAs)
Salivary miRNAs have recently been identified as the most promising biomarker in the identification of concussion in sport. miRNAs are non-coding fragments of RNA that

Figure 1  Concussion in Sport Group definition of concussion and American Congress of Rehabilitation Medicine definition of mTBI. GCS, Glasgow Coma Scale; LOC, loss of consciousness; mTBI, mild traumatic brain injury; PTA, post-traumatic amnesia.
play an important role in gene expression.\(^8\) The most significant study so far in the investigation of salivary miRNA was the Study of Concussion in Rugby Union through MicroRNAs or ‘SCRUM study’, results of which were published in 2021. This study found that a panel of 14 miRNAs successfully identified concussed rugby players from those with a negative concussion assessment, non-injured controls and musculoskeletal injured controls. The miRNA panel was able to differentiate concussed participants from the other groups immediately after the game (area under the curve (AUC) 0.91, 95% CI 0.81 to 1.0) and 36–48 hours later (AUC 0.94, 95% CI 0.86 to 1.0).\(^9\) These findings have significant implications for use in professional sports. Therefore, it may be of use in non-athletes to detect concussion in the ED. Salivary miRNAs are worthy of further investigation in the non-athlete setting where there are far greater variations in age and physical and cognitive baseline characteristics of patients presenting with a head injury.

**Sports Concussion Assessment Tool, Fifth Edition**

The SCAT5 is the most recent version of the SCAT, based on a systematic review of recent research and expert panel input as part of the Fifth International Consensus Conference on Concussion in Sport held in Berlin in 2016.\(^1\) The SCAT5 is a widely used tool used in the assessment of sports-related concussion (SRC) in patients 13 years or older and should take no less than 10 min to perform. The diagnostic utility of the SCAT decreases after 3–5 days and has limited utility in tracking the recovery of patients.\(^1,6\) The assessment should be conducted by healthcare professionals only and is not designed to be a stand-alone tool in the diagnosis of concussion.

Very few studies using SCAT in non-athlete populations have been published most data coming from adolescent athletes. A shared finding across non-athlete studies is that symptom number and severity seem to provide the most diagnostic accuracy for discriminating between concussed and control patients.\(^10–14\) The balance assessment is not well tolerated in non-athletes\(^15\) and poses obvious problems where the control sample have suffered limb injury. Very few studies have reported individual elements of the SCAT assessment, with the majority combining all non-symptom sections of the test to provide a Standardised Assessment of Concussion score.

**Immediate Post-Concussion Assessment and Cognitive Testing**

The ImPACT is a computer-based neurocognitive assessment widely used of professional sports.\(^7\) The ImPACT should be administered by a healthcare professional and validated for patients aged 12–59 years. The test should take 20–25 min to administer and considers several different assessment domains. As with the SCAT5, the ImPACT is not designed to be used as a stand-alone diagnostic tool. The ImPACT provides composite domain scores for verbal memory, visual memory, reaction time, processing speed and impulse control. Details of specific tests and how composite scores are calculated are included in table 1.

This requires a pre-injury assessment to which post-concussion scores are compared. The program calculates a Reliable Change Index score and, where this exceeds the expected range in variation, identifies it as abnormal.\(^7\) The ImPACT Quick program was designed for use at the pitch side and to aid in removal-from-play decisions. Rather than relying on a pretest score to compare, the results are presented as percentile scores from a large representative sample of individuals with no history of concussion.

A recent literature review examining the validity of the ImPACT revealed that although the tool demonstrated sound convergent validity, research describing discriminant validity and diagnostic accuracy was either inconclusive or scanty.\(^15\) This provides support for further studies in this area. Very few of the studies included in the review concerned the use of the ImPACT in non-athlete populations, and 3 of the 69 studies analysed the use of the ImPACT in concussed versus controls suffering orthopaedic injuries.

Non-athlete studies using the ImPACT have produced conflicting results. A 2017 American study recruited 94 concussed patients and 80 matched-trauma controls from ED and performed the ImPACT within 72 hours of injury, 15 days and 45 days.\(^16\) No significant difference in composite scores was found between groups at any of the time points. By comparison, an Australian study assessing 79 concussed patients to 86 trauma control patients in

| Table 1 | ImPACT composite score calculations |
| --- | --- |
| **ImPACT composite score** | **Calculation** |
| Verbal memory | Average of these scores |
|  | ► Word memory total per cent correct (immediate+delay)/2. |
|  | ► Symbol match (hidden symbols)/9×100. |
|  | ► Three letters total letters correct. |
| Visual memory | Average of the following scores |
|  | ► Xs and Os−total correct (interference) total/4. |
|  | ► Design memory−total per cent correct (immediate+delay)/2. |
| Reaction time | Average of these scores |
|  | ► Xs and Os average correct RT. |
|  | ► Symbol match average correct RT/3. |
|  | ► Colour match average correct RT. |
| Processing speed | Average of the following scores |
|  | ► Xs and Os−total correct (interference) total/4. |
|  | ► Three letters−average correctly×3. |
| Impulse control | Sum of the following scores |
|  | ► Xs and Os−total incorrect−interference. |
|  | ► Colour match total commissions. |

\(^1\) Toman E, et al. BMJ Open 2022;12:e062030. doi:10.1136/bmjopen-2022-062030
the ED found significant differences in all five composite domain scores.  

**RATIONALE**

Previous work suggests that concussion remains underdiagnosed in the ED and patients may not be followed up adequately in clinical practice. This may reflect the complex nature of diagnosing and monitoring concussion but may also demonstrate the lack of NHS resources allocated towards concussion care. Additional common barriers to screening for concussion in NHS patients such as intoxication and dementia complicate recognition and diagnosis further. It is important therefore to assess whether well-established SRC assessment tools may be translated into the non-sporting population of the NHS. A longer-term qualitative review of the tools would add depth to existing data and also indicate the willingness of non-athletes to engage in these tests using telephone and email reviews.

Currently, the National Institute for Health and Care Excellence guidelines concerning head injury focus on appropriate triage and acute management. No guidelines exist regarding follow-up or referral of patients with ongoing symptoms. More innovative ways of monitoring recovery and symptoms in such patients need to be developed, ideally remotely. A concussion assessment that is clinically accurate and that patients can—and want to—perform at home could revolutionise the possibilities in which secondary care clinicians could manage these patients.

**METHODS AND ANALYSIS**

**Study design**

Concussion in Non-athletes: Assessment of Cognition and Symptomatology is a prospective cohort study investigating the use of sports concussion assessment tools and the diagnostic utility of salivary miRNAs in concussed versus control adult participants following non-sporting maxillofacial trauma. It will commence with a phase I feasibility study followed by a phase II substantive study if progression criteria are met. Both phases will take place at the Queen Elizabeth Hospital Birmingham as a single-centre study. Participants will be followed up for 6 months post recruitment. Phase I commenced on 21 July 2021, and the planned end date for recruitment to all study phases is 1 October 2023.

Patients of interest are 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. This also provides a sample of patients who require admission to hospital, whereas isolated concussion does not usually require admission to the hospital.

**Eligibility criteria**

For patients with isolated concussion, the standard clinical care would be discharge from the ED with a responsible adult and suitable head injury advice. To optimise the rate of follow-up of participants, only patients requiring admission will be recruited. To ensure that all participants in the concussion arm have suffered an impact to the head, face or neck (as required for concussion diagnosis according to CISE definition), only patients with maxillofacial injury will be recruited. Brain imaging is not an inclusion criterion as not all patients suffering from concussion require CT scanning, and we wish to reflect clinical practice in this pragmatic study design. The control arm will consist of participants having suffered an isolated limb injury. Inclusion and exclusion criteria are summarised in **table 2**.

This is an observational study, and therefore, there will be no study-related interventions in the clinical care of participants. The SCAT5 and ImPACT tools will be used by study investigators to assess participants in addition to their routine clinical care. Salivary sample collection is a non-invasive procedure.

Concussed participants will be compared with participants who had sustained isolated limb trauma as controls. Patients with isolated limb injuries are a suitable control group because they have similar Abbreviated Injury Scale severity codes to concussion and facial injuries. Isolated lower limb injuries requiring admission will also receive management similar to that of the concussed group such as operative interventions and pain management.

**Patient and public involvement**

A consultation with Patient and Public Involvement and Engagement (PPIE), the Trauma Advisory Group (TAG) (previously known as the Accident, Burns and Critical Care group) of the National Institute for Health Research, Surgical Reconstruction and Microbiology Research Centre, was undertaken in June 2018. The TAG consists of around 20 members and is a collective of patients, family and members of the public with a mixed experience of trauma, burns and critical care. The age and sex of members ranges from mid-20s to retirement, and the majority have been involved in clinical research studies.

Overall, there was very positive feedback from the group about the study. Members who have been involved in previous clinical studies stated they liked the study design and expressed interest in joining the study if they or members of their families were approached. Specifically, the group felt that the time required to complete study assessments as a participant was reasonable and not too onerous.

**Feasibility phase and progression criteria**

The feasibility phase (phase I) aims to recruit 30 patients within 6 months. Phase I will end after 6 months or following the 14-day postinjury time point of participant 30, whichever comes sooner. Following the completion of phase I, the study management group will meet to assess and attribute a red, amber or green status to the study:

- **Red**: intractable issues that cannot be remedied; study should not progress to phase II.
Amber: remediable issues that require attention before progressing to phase II.
Green: no concerning issues that threaten the success of the trial; continue to phase II without substantial amendment (minor amendments may be required).

Progression criteria are listed as follows:

► The target recruitment rate is five participants per month. If fewer than 70% of the target recruitment number (21 patients) has been recruited by month 6 of phase I without identifiable and correctable cause, it would not be feasible to progress to phase II.
► Following phase I, if the loss to follow-up at the 24–48 hours and 14-day time points exceed 30% in either arm without identifiable and correctable cause, it would not be feasible to progress to phase II without substantial amendments to the study design.

STUDY PROCEDURE
A summary of the eligibility criteria and recruitment process is contained in figure 2.

Participant identification
The research team will approach the potential participant only once eligibility has been confirmed by the treating clinical (either oral and maxillofacial or trauma and orthopaedics) teams.

Screening
Discussion with the treating clinical team should confirm that the patient will require hospital admission, and there is a diagnosis of either maxillofacial injury or isolated limb injury. Any CT head scan reports performed as a standard of clinical care must be reviewed to confirm the presence or absence of intracranial injury (according to the eligibility criteria). To confirm a diagnosis consistent with a concussion, the CSG definition of concussion¹ and the ACRM² definition of mTBI must be met.

Consent
When potential participants fulfil eligibility criteria, they will be approached by a member of the research team who will provide the patient information sheet and clarify any information from the patient/relatives that may prevent recruitment. Wherever possible, informed consent will be obtained from the patient; however, due to the nature of the concussion, this may not be possible.

The process for obtaining consent from patients lacking capacity is outlined further.

Patient personal consultee available in hospital
For patients lacking capacity, a personal consultee will be sought. If such a consultee is available in the hospital, they will be provided with written information about the study and asked if they wish to provide written agreement prior to enrolment.

Patient personal consultee not available in the hospital
For patients lacking capacity where no personal consultee is available in the hospital, enrolment will be possible with a written agreement from a nominated consultee. If a
personal consultee becomes available, then the study will be discussed with them and a written agreement will be gained for the participant to continue in the study.

Patients who regain capacity
Where patients regain capacity following either personal or nominated consultee agreement, they will be informed about the study and asked for consent to continue as a participant.

If at any time either the personal consultee or the participant chooses to withhold consent or written agreement, then the participant will be withdrawn from the study. An agreement with the participant or the personal consultee will be made at this time point as to whether they give permission for the use of any data already collected as part of the study or whether they wish for this to be destroyed. If the data have been analysed, it will not be able to be destroyed and the participant will be informed.

Personal consultee definition
A personal consultee is an individual who knows the patient well but is not acting in a professional or paid capacity and someone whom the person who lacks capacity would trust with important decisions about their welfare, for example, a family member or close friend.
Table 3  Baseline data to be collected in the emergency department

| Standard of care                  | Patient demography Medical history (including comorbidities and medications) Injury-related events (time of injury, mechanism of injury and subsequent signs/symptoms) Neurological status Diagnosed injury CT head findings (only if performed as standard of care) Medications received |

Study-related data

| ImPACT Quick | SCAT5 Contact details (telephone and email address) Educational level (number of years of education completed) Diagnosis of learning disability or attention deficit hyperactivity disorder Level of intoxication (number of units of alcohol consumed as reported by the participant) History of concussion or other head injury |

Table 4  Summary of study assessments at 24–48 hours, 14 days and 6 months

| 24–48 hours | ImPACT SCAT5 Operative interventions Neurological status Presence or absence of PTA CT head findings (only if performed as standard of care) saliva sample |

| 14 days     | ImPACT performed remotely (link sent via email) SCAT5 symptoms checklist (via telephone) |

| 6 months    | SCAT5 symptoms checklist (via telephone) Functional data (return to work, return to fitness) |

ImPACT, Immediate Post-Concussion Assessment and Cognitive Testing; SCAT5, Sports Concussion Assessment Test, Fifth Edition.

Nominated consultee definition

A nominated consultee is an independent healthcare professional who is prepared to be consulted by the researcher but has no connection with the research study.

Baseline and study assessment data

All participants will have a medical history and clinical examination as part of routine standard of care, and the following will be recorded in the case report form. Tables 3 and 4 contain summaries of relevant baseline data and study assessment to be collected at time points in the ED, at 24–28 hours, 14 days and 6 months.

No specific study 'test conditions' will be imposed during the study assessments to continue the pragmatic nature of the study. Study assessments will be conducted in a real-life clinical environment to provide a true reflection of the translatable nature of any study results.

Qualitative assessment

A qualitative telephone interview will be conducted at 6 months following enrolment. As suggested by the TAG PPI group, where possible, the interviewer will be the same researcher who has had prior contact with the patient, either in-hospital or via telephone. The format will be of ‘in-depth semistructured’ interviews on an individual basis. These are interviews organised around a set of predetermined open-ended questions, with other questions generated from a subsequent dialogue between the interviewer and the interviewee. The interviews will be conducted via telephone and recorded for subsequent analysis using NVivo analysis software.

Collection, storage and testing of saliva samples

The samples will be collected in OCR-100 saliva collection pots containing a proprietary miRNA stabilising solution. Saliva is collected using a standardised technique where the user gently rubs the sponge swab along the lower gums 10 times on either side of the mouth. In these pots, samples will be stable at room temperature for 8 weeks and will be transferred to the laboratory within 1 week of collection to comply with Human Tissue Act regulations. The samples will be transported to the laboratory at the University of Birmingham (UoB) and stored in the −80° freezer. The miRNA profile will be analysed using standard quantitative PCR technique. Once the study has been completed all samples will be destroyed.

Sample size calculation

As phase I is an exploratory cohort study, no formal sample size calculation has been performed. Following recommendations for pilot studies, 30 patients or more are typically required to obtain estimates of the parameters needed for sample size estimation. Hence, phase I of this study will aim to recruit 30 patients to estimate the mean and SD of the seven SCAT5 domain scores and three composite ImPACT Quick domain scores in the ED. This will also allow the recruitment and retention rates to be estimated with 95% CI maximum widths of 27% and 35%, respectively.

The sample size for phase II will be calculated based on the observed distributions of outcome scores in phase I.

Statistical analysis plan

The data analysis for phase I will be descriptive and will focus on CI estimation, with no hypothesis testing performed. Data will be explored to assess the key feasibility aspects of undertaking a full-scale study on the clinical accuracy of concussion assessment tools in patients with non-sporting trauma.
Dichotomous feasibility measures, such as the recruitment and retention rates, as well as data completeness, will be reported as numbers and percentages. Where appropriate, these values will be summarised across patient groups.

Phase I data will inform the selection of the primary outcomes for the main study and provide estimates for sample size calculations. Outcome data on concussion assessment tools are collected in the ED, at 24–48 hours, 14 days and 6 months post recruitment. Analysis methods will be chosen according to the data type of the outcome under investigation, in brief,

- **Continuous endpoints** (e.g., SCAT5 domain scores): These data will be summarised using means and SD, with differences in means with 95% CIs reported. Longitudinal plots of the data over time will also be constructed for visual presentation of the data.
- **Time to event endpoints** (e.g., time to return to work or recovery): The numbers of participants and percentages experiencing the event will be summarised over time between groups. Kaplan-Meier curves will be constructed for visual presentation of time-to-event data.

The phase II data will be used to undertake exploratory analyses of concussion assessment tool domains adjusted for baseline demographics (age, education level and gender) and level of self-reported intoxication.

**Primary outcome analysis (phase I)**
The scores in the three ImPACT Quick domains (speed, memory and attention) and seven SCAT5 domains (symptoms number, symptom severity, orientation, immediate memory, concentration and balance errors) will be summarised across the concussed and control groups in ED. These are continuous outcomes, and a linear regression model adjusting for gender, educational level, age and intoxication level will be used to calculate the adjusted mean differences and 95% CIs. Unadjusted models will be used in the event of the adjusted models failing to converge.

**Secondary outcome analysis (phase III)**
Continuous data (e.g., ImPACT and SCAT5 domain scores at specified time points) will be analysed in the same way as the primary outcome. The panel of 23 salivary miRNAs will be analysed as continuous data in the same way as the primary outcome but using a Benjamin-Hochberg procedure to control the false discovery rate when testing these multiple hypotheses. Time-to-event data (e.g., time to recovery) will be analysed using the log-rank test with a Cox proportional hazard model used to calculate HRs, if the assumptions of proportionality are met.

**Qualitative analysis**
Interview data will be audio recorded for analysis using an encrypted audio recorder device. Formal analysis will be performed using NVivo qualitative data analysis software. Thematic analysis will be used, and some anonymised quotes will be included in the final report. Qualitative data will be reported according to Consolidated Criteria for Reporting Qualitative research guidelines.25

**ETHICS AND DISSEMINATION**
All study related data collected will be stored on NHS servers in accordance with the 1998 UK Data Protection Act, UoB and University Hospitals Birmingham NHS Foundation Trust data handling and maintenance guidelines. The Trust network has restricted physical access; data are stored under coded file names, and the local network has secure password access restricted to researchers involved with the study.

The study investigators intend to submit their study findings for publication in peer reviewed journals and to disseminate the findings via presentation at academic meetings/conferences. The results will also form part of a doctorate thesis registered at the UoB.

Ethical approval was granted in February 2021 (ref 20/WM/0299) by the West Midlands Coventry & Warwickshire Research Ethics Committee.

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ET, JB, AB, VDP and LC contributed to the study design. ET, RW and DH edited the study design. ET, MR, DNN, VD, SH and KMY contributed to manuscript preparation and editing. All authors agreed on the final manuscript edit prior to submission.

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**Competing interests**
AB and VDP are members of the research team and shareholders for Marker Diagnostics, the company providing the funding for the saliva microRNA tests.

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

**Patient consent for publication**
Not applicable.

**Provenance and peer review**
Not commissioned; externally peer reviewed.

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