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The CONcussion in non-aThletes; Assessment of CogniTion and Symptomatology (CONTACTS) study: An exploratory cohort study investigating the utility of sports concussion assessment tools and salivary micro-RNAs to diagnose concussion in NHS patients

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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 micro-RNAs (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 NHS patients, and whether well-established sports-related concussion (SRC) assessment tools may be translated into the Emergency Department (ED).

Methods and analysis:

CONTACTS 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. Saliva samples will be taken to identify the presence of miRNAs. The SRC assessments being investigated include the Sports Concussion Assessment Test version 5 (SCAT5), the Immediate Post-Concussive Assessment and Cognitive Test (ImPACT) and the ImPACT Quick. Follow up will be at 24-48 hours, 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).

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
- Inclusion of older patients and those with mental health conditions or concurrent intoxication
- COVID may limit the amount of time patients are in ED and so the design may need to be adapted
- Those with premorbid neurological or cognitive issues were unable to be included in this study

INTRODUCTION

Background and previous literature:

Concussion is defined as "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces". (1) Signs and symptoms are nonspecific and are largely categorised into physical, cognitive, behavioural and sleep. The Concussion in Sport Group (CISG) provides a clear definition of concussion with clinical criteria that are summarised in Figure 1. (1)

Each year 1.4 million people present to the Emergency Department (ED) in England and Wales with traumatic brain injury (TBI). (2) Since 90% of TBI cases are classified as mild in severity (3) and have an estimated lifetime cost of $5,299, (4) 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 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. (1) Two such widely accepted tools include the paper-based Sports Concussion Assessment Tool 5th edition (SCAT5) (5) and the computerised neurocognitive Immediate Post-Concussive Assessment and Cognitive Test (ImPACT). (6) 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 be applicable to the overall NHS population presenting to services with concussion.

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 play an important role in gene expression. (7) The most significant study so far in the investigation of salivary miRNA was the Study of Concussion in Rugby Union through MicroRNAs; the "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 between clinically-diagnosed concussion and clinically-excluded concussion immediately post-match and at 36-48 hours which has significant implications for use in professional sports. (8) It also demonstrates great promise for use in non-athletes in the detection of concussion in the ED. Salivary miRNAs are worthy of further investigation in the non-athlete setting where there is a far greater variation in age, physical and cognitive baseline characteristics of patients presenting with head injury.

Sports Concussion Assessment Tool 5th edition (SCAT5)

The SCAT5 is the most recent version of the SCAT, based on a systematic review and synthesis of current research, public input and expert panel review as part of the 5th International Consensus Conference on Concussion in Sport held in Berlin in 2016. (1) The SCAT5 is validated for assessment of sports-related concussion in patients 13 years or older and should take no less than 10 minutes to perform. The assessment should be conducted by healthcare professionals only and is not designed to be a standalone tool in the diagnosis of concussion.

Very few studies using SCAT in non-athlete populations have been published with the vast majority of 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. (9-13) The balance assessment is not well tolerated in non-athletes (11) 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 (SAC) score.

Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

The ImPACT tool is a computer-based neurocognitive assessment widely used across a variety of professional sports. (6) The test should be administered by a healthcare professional and is validated for patients aged 12-59 years. The test should take 20-25 minutes to administer and considers several different assessment domains. As with the SCAT5, the ImPACT tools are not designed to be used as a standalone diagnostic tool. The ImPACT tool includes multiple tests culminating in scores for verbal memory, visual memory, reaction time, processing speed, impulse control and total symptom score.

A recent literature review examining the validity of the ImPACT test revealed that although the tool demonstrated sound convergent validity, research describing discriminant validity and diagnostic accuracy was either inconclusive or scanty. (14) This provides support for further studies in this area. Very few of the studies included in the review concerned the use of ImPACT in non-athlete populations and three of the sixty-nine studies analysed the use of ImPACT in concussed versus controls suffering orthopaedic injuries.

Non-athlete studies using the ImPACT assessment have produced conflicting results. A 2017 American study recruited 94 concussed patients and 80 matched-trauma controls from ED and performed ImPACT assessment within 72 hours of injury, 15 days and 45 days. (15) No significant difference in

composite scores were found between groups at any of the time points. By comparison, an Australian study assessing 79 mild TBI (mTBI) patients to 86 trauma control patients in the ED found significant differences in all 5 composite domain scores. (16)

RATIONALE

Previous work suggests that concussion remains underdiagnosed in the ED (17, 18) and patients may not be followed up adequately in clinical practice. (19) This may reflect the complex nature of diagnosing and monitoring concussion but may also demonstrate the lack of NHS resources allocated towards mTBI care. Additional common barriers to screening for concussion in NHS patients such as intoxication and dementia complicate recognition and diagnosis further. (17) It is important therefore to assess whether well-established SRC assessment tools may be translated into the non-sporting population of the NHS. To determine whether these tools can be translatable, they must be tested in groups that are reflective of the patients who suffer concussive injury in the NHS population. Therefore, elderly and intoxicated patients should also be assessed. A longer-term qualitative review of the tools would add depth to existing data and 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 (NICE) guidelines concerning mTBI/concussion focus on appropriate triage and acute management of head injury. 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

CONTACTS 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 1, feasibility study followed by a phase 2, substantive study if progression criteria are met. Both phases will take place at the Queen Elizabeth Hospital Birmingham (QEHB) as a single-centre study. Participants will be followed up for a period of 6 months post recruitment.

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.

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 CISG definition), only patients with maxillofacial injury will be recruited. The control arm will consist of participants having suffered an isolated limb injury. Inclusion and exclusion criteria are summarised in table 1.

Table 1. Summary of eligibility criteria for the CONTACTS study

Cohort	Inclusion	Exclusion

Both	≥16 years old Requires admission to QEHB Injury sustained within 24 hrs of presentation	Police custody Prisoner Evidence of intracranial injury on CT (if performed as part of standard clinical care) Significant communication barriers Not fluent in English language Prior medical history of neurological or cognitive impairment
Concussed	Diagnosis of maxillofacial injury Clinical features consistent with diagnosis of concussion: - History of direct blow to the head, face, neck or elsewhere on the body with an ''impulsive'' force transmitted to the head - History of rapid onset of short-lived impairment of neurologic function that resolves spontaneously - No evidence of structural abnormality to the brain seen on standard neuroimaging - LOC ≤ 30 minutes - GCS ≥ 13 on presentation - PTA ≤ 24 hrs	LOC > 30mins GCS < 13 on presentation PTA lasting > 24 hrs (assess at 24 hrs) Mechanism of injury due to organised sports activity
Control	Diagnosis of isolated limb injury	History of TBI Clinical features consistent with diagnosis of concussion according to CISG criteria and ACRM definition Insufficiency, open, femoral or tibia-fibula fracture

LOC (loss of consciousness), GCS (Glasgow Coma Scale), PTA (post traumatic amnesia)

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.

Patients of interest will be compared to patients who had sustained isolated limb trauma as controls. 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.

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 (NIHR SRMRC) was undertaken in June 2018. The TAG consists of around 20 members and are a collective of patients, family and members of the public with a mixed experience of trauma, burns and critical care. The age of members ranges from mid-twenties 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 1) aims to recruit 30 patients within 6 months. Phase 1 will end after 6 months or following the 14-day post-injury time-point of participant number 30—whichever comes

sooner. Following the completion of phase 1, 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 2

Amber: remediable issues that require attention prior to progressing to phase 2

Green: no concerning issues that threaten the success of the trial; continue to phase 2 without substantial amendment (minor amendments may be required).

Progression criteria are listed below:

1. The target recruitment rate is 5 participants per month. If fewer than 70% of the target recruitment number (21 patients) have been recruited by month 6 of phase 1 without identifiable and correctable cause it would not be feasible to progress to phase 2.
2. Following phase 1, if loss to follow up at the 24-48 hrs and 14-day time-points exceeds 30% in either arm without identifiable and correctable cause, it would not be feasible to progress to phase 2 without substantial amendments to 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 computerised tomography (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 concussion the CISG definition of concussion (1) and the American Congress of Rehabilitation Medicine (ACRM) (20) definition of mTBI must be met.

Consent

Where 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 concussion, this may not be possible.

The process for obtaining consent in patients lacking capacity is outlined below:

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 written agreement from a nominated consultee. If a personal consultee becomes available, then the study will be discussed with them and written agreement 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 participant choose to withhold consent or written agreement, then the participant will be withdrawn from the study. An agreement with the participant or 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 has been analysed, it will not be able to be destroyed and the participant will be informed.

Personal consultee definition

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.

Nominated consultee definition

An independent healthcare professional (IHP) 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 (CRF). Tables 2 and 3 contain summaries of relevant baseline data and study assessment to be collected at timepoints in the ED, at 24-28hours, 14 days and 6 months.

Table 2. Baseline data to be collected in the Emergency Department

Standard of care	Patient demography
	Past medical history (including co-morbidities and medications)
	Injury related events (time of injury, mechanism of injury, 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
Study related sample	Saliva sample

Table 3. Summary of study assessments at 24-48h, 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)

Qualitative assessment

A qualitative telephone interview will be conducted at 6 months following enrolment. As suggested by the TAG PPIE 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 semi-structured" interviews on an individual basis. These are interviews organised around a set of predetermined open-ended questions, with other questions generated from subsequent dialogue between interviewer and interviewee. (21) 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-100saliva collection pots containing a proprietary miRNA stabilising solution. 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 degrees freezer. miRNA profile will be analysed using standard qPCR technique. Once the study has been completed all samples will be destroyed.

Sample size calculation

As phase 1 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. (22, 23) Hence, phase 1 of this study will aim to recruit 30 patients to estimate the mean and SD of the 7 SCAT5 domain scores and 3 composite ImPACT Quick domain scores in the ED. This will also allow the recruitment and retention rates to be estimated with 95% confidence interval maximum widths of 27% and 35% respectively.

The sample size for phase 2 will be calculated based on the observed distributions of outcome scores in phase 1.

Statistical analysis plan

The data analysis for phase 1 will be descriptive and mainly focus on confidence interval 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.

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. Outcome data on concussion assessment tools are collected in 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 standard deviations, with differences in means with 95% confidence intervals 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 2 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 1)

The scores in the three ImPACT Quick domains (speed, memory and attention) and 7 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 models adjusting for gender, educational level, age, and intoxication level, will be used to calculate the adjusted mean differences and 95% confidence intervals. Unadjusted models will be used in the event of the adjusted models failing to converge.

Secondary outcome analysis (Phase 2)

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 Benjamini-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 hazard ratios, 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 (COREQ) guidelines. (24)

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 University of Birmingham.

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

CONTRIBUTIONS

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

FUNDING COMPETING INTERESTS

Prof A Belli and Dr V Di Pietro are members of the research team and shareholders for Marker Diagnostics ltd, the company providing the funding for the salivary miRNA tests.

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FIGURE LEGENDS

Figure 1. CISG definition of concussion

Figure 2. Study protocol flowsheet

- History of direct blow to the head, face, neck or elsewhere on the body with an ''impulsive'' force transmitted to the head
- History of rapid onset of short-lived impairment of neurologic function that resolves spontaneously
- No evidence of structural abnormality to the brain seen on standard neuroimaging
- LOC for no longer than 30 minutes
- GCS of 13 or higher on presentation
- PTA for no longer than 24 hrs

CISG: Concussion in Sport Group; LOC: loss of consciousness; GCS: Glasgow Coma Scale; PTA: post-traumatic amnesia

Figure 1. CISG definition of concussion

221x109mm (192 x 192 DPI)

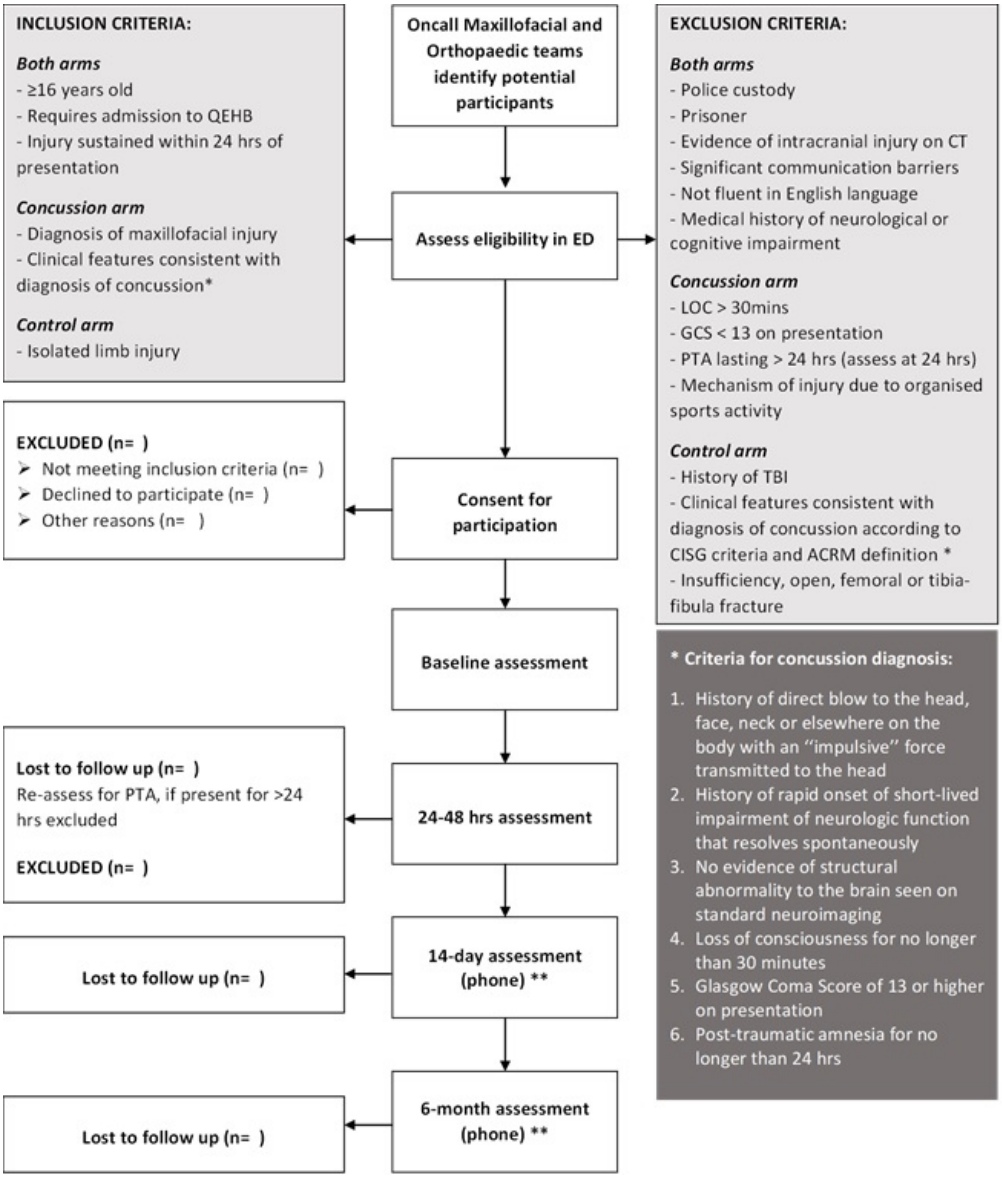

Figure 2. Study protocol flowsheet

86x101mm (192 x 192 DPI)

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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

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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 micro-RNAs (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 (NHS) patients, and whether well-established sports-related concussion (SRC) assessment tools may be translated into the Emergency Department (ED).

Methods and analysis:

CONTACTS 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 version 5 (SCAT5), the Immediate Post-Concussive Assessment and Cognitive Test (ImPACT), and the ImPACT Quick. Follow-up will be at 24-48 hours in-hospital and remotely via telephone and email at14 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, those suffering from mental health conditions and concurrent intoxication) are to be included, to improve the translation into clinical practice
- COVID may limit the amount of time patients are in ED 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
- Patients discharged home from ED are not included in the study design

INTRODUCTION

Background and previous literature:

Concussion is defined as "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces". (1) Signs and symptoms are nonspecific 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. (1, 2)

Each year 1.4 million people present to the Emergency Department (ED) in England and Wales with traumatic brain injury (TBI). (3) Since 90% of TBI cases are classified as mild in severity (4) and have an estimated lifetime cost of $5,299, (5) 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. (1) Two such widely accepted tools include the paper-based Sports Concussion Assessment Tool 5th edition (SCAT5) (6) and the computerised neurocognitive Immediate Post-Concussive Assessment and Cognitive Test (ImPACT). (7) 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 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; the "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 (AUC 0.91, 95% CI 0.81 to 1) and 36–48 hours later (AUC 0.94, 95% CI 0.86 to 1). (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 a far greater variation in age, and physical and cognitive baseline characteristics of patients presenting with a head injury.

Sports Concussion Assessment Tool 5th edition (SCAT5)

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 5th 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 in patients 13 years or older and should take no less than 10 minutes to perform. The diagnostic utility of the SCAT decreases after 3–5 days and has limited utility in tracking the recovery of patients. (6) The assessment should be conducted by healthcare professionals only and is not designed to be a standalone 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 (12) 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 (SAC) score.

Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

The ImPACT is a computer-based neurocognitive assessment widely used of professional sports. (7) The ImPACT should be administered by a healthcare professional and is validated for patients aged 12-59 years. The test should take 20-25 minutes to administer and considers several different

assessment domains. As with the SCAT5, the ImPACT is not designed to be used as a standalone 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.

Table 1. ImPACT composite score calculations

ImPACT composite score	Calculation
Verbal memory	Average of these scores: • Word Memory total percent correct (immediate + delay) / 2 • Symbol Match (hidden symbols)/9*100 • Three letters Total letters correct
Visual memory	Average of the following scores: • X's and 0's-total correct (interference) total/4 • Design memory-total percent correct (immediate + delay) / 2
Reaction time	Average of these scores: • X's and 0's average correct RT • Symbol Match average correct RT/3 • Colour Match average correct RT
Processing speed	Average of the following scores: • X's and 0's-total correct (interference) total/4 • Three letters-average counted correctly*3
Impulse control	Sum of the following scores: • X's and 0's-total incorrect –interference • Colour match total commissions

This requires a pre-injury assessment to which post-concussion scores are compared. The program calculates a reliable change index (RCI) score and where this exceeds the expected range in variation, identifies it as abnormal. (7) The ImPACT Quick programme was designed for use at the pitch side and

to aid in removal-from-play decisions. Rather than relying on a pre-test 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 three of the sixty-nine 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 were found between groups at any of the time points. By comparison, an Australian study assessing 79 concussed patients to 86 trauma control patients in the ED found significant differences in all 5 composite domain scores. (17)

RATIONALE

Previous work suggests that concussion remains underdiagnosed in the ED (18, 19) and patients may not be followed up adequately in clinical practice. (20) 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. (18) 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 (NICE) 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

CONTACTS 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 1, feasibility study followed by a phase 2, substantive study if progression criteria are met. Both phases will take place at the Queen Elizabeth Hospital Birmingham (QEHB) as a single-centre study. Participants will be followed up for 6 months post recruitment. Phase 1 commenced on 21/07/2021 and the planned end date for recruitment to all study phases is 01/10/2023.

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 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 CISG 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 (3) 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.

Table 2. Summary of eligibility criteria for the CONTACTS study

Cohort	Inclusion	Exclusion
Both	≥16 years old	Police custody
	Requires admission to QEHB	Prisoner
	Injury sustained within 24 hrs of presentation	Evidence of intracranial injury on CT (if performed as part of standard clinical care)
		Significant communication barriers
		Not fluent in the English language
		Prior medical history of neurological or cognitive impairment
Concussed	Diagnosis of maxillofacial injury	LOC > 30mins
	Clinical features consistent with a diagnosis of concussion: - History of direct blow to the head, face, neck, or elsewhere on the body with an ''impulsive'' force transmitted to the head - History of rapid onset of short-lived impairment of neurologic function that resolves spontaneously - No evidence of structural abnormality to the brain seen on standard neuroimaging - LOC ≤ 30 minutes - GCS ≥ 13 on presentation - PTA ≤ 24 hrs	GCS < 13 on presentation
		PTA lasting > 24 hrs (assess at 24 hrs)
		Mechanism of injury due to organised sports activity
Control	Diagnosis of isolated limb injury	History of TBI
		Clinical features consistent with a diagnosis of concussion according to CISG criteria and ACRM definition
		Insufficiency, open, femoral, or tibia-fibula fracture

LOC (loss of consciousness), GCS (Glasgow Coma Scale), PTA (post-traumatic amnesia)

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 to 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 (AIS) severity codes to concussion and facial injuries. (21) Isolated lower limb injuries requiring admission will also receive similar management to 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 (NIHR SRMRC) 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 of members ranges from mid-twenties 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 1) aims to recruit 30 patients within 6 months. Phase 1 will end after 6 months or following the 14-day post-injury time-point of participant number 30—whichever comes sooner. Following the completion of phase 1, 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 2

Amber: remediable issues that require attention before progressing to phase 2

Green: no concerning issues that threaten the success of the trial; continue to phase 2 without substantial amendment (minor amendments may be required).

Progression criteria are listed below:

1. The target recruitment rate is 5 participants per month. If fewer than 70% of the target recruitment number (21 patients) have been recruited by month 6 of phase 1 without identifiable and correctable cause it would not be feasible to progress to phase 2.
2. Following phase 1, if the loss to follow up at the 24-48 hrs and 14-day time-points exceed 30% in either arm without identifiable and correctable cause, it would not be feasible to progress to phase 2 without substantial amendment nts to 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 computerised tomography (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 CISG definition of concussion (1) and the American Congress of Rehabilitation Medicine (ACRM) (2) 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 concussion, this may not be possible.

The process for obtaining consent in patients lacking capacity is outlined below:

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 written agreement from a nominated consultee. If a personal consultee becomes available, then the study will be discussed with them, and written agreement 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 participant choose to withhold consent or written agreement, then the participant will be withdrawn from the study. An agreement with the participant or 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

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.

Nominated consultee definition

An independent healthcare professional (IHP) 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 (CRF). Tables 3 and 4 contain summaries of relevant baseline data and study assessment to be collected at timepoints in the ED, at 24-28hours, 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 the real-life clinical environment to provide a true reflection of the translatability of any study results.

Table 3. Baseline data to be collected in the Emergency Department

Standard of care	Patient demography
	Past medical history (including co-morbidities and medications)
	Injury related events (time of injury, mechanism of injury, 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
Study related sample	Saliva sample

Table 4. Summary of study assessments at 24-48h, 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)

Qualitative assessment

A qualitative telephone interview will be conducted at 6 months following enrolment. As suggested by the TAG PPIE 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 semi-structured" interviews on an individual basis. These are interviews organised around a set of predetermined open-ended questions, with other questions generated from subsequent dialogue between interviewer and interviewee. (22) 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 ten 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 degrees freezer. miRNA profile will be analysed using standard qPCR technique. Once the study has been completed all samples will be destroyed.

Sample size calculation

As phase 1 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. (23, 24) Hence, phase 1 of this study will aim to recruit 30 patients to estimate the mean and SD of the 7 SCAT5 domain scores and 3 composite ImPACT Quick domain scores in the ED. This will also allow the recruitment and retention rates to be estimated with 95% confidence interval maximum widths of 27% and 35% respectively.

The sample size for phase 2 will be calculated based on the observed distributions of outcome scores in phase 1.

Statistical analysis plan

The data analysis for phase 1 will be descriptive and mainly focus on confidence interval 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 1 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 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 standard deviations, with differences in means with 95% confidence intervals 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 2 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 1)

The scores in the three ImPACT Quick domains (speed, memory and attention) and 7 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% confidence intervals. Unadjusted models will be used in the event of the adjusted models failing to converge.

Secondary outcome analysis (Phase 2)

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 hazard ratios, 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 (COREQ) 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 University of Birmingham.

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

CONTRIBUTIORSHIP

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

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COMPETING OF INTERESTS

Prof A Belli and Dr V Di Pietro are members of the research team and shareholders for Marker Diagnostics ltd, the company providing the funding for the salivary miRNA tests.

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FIGURE LEGENDS

Figure 1. CISG definition of concussion and ACRM definition of mTBI

Figure 2. Study protocol flowsheet

Concussion in Sport Group definition of concussion

- History of direct blow to the head, face, neck or elsewhere on the body with an ''impulsive'' force transmitted to the head
- History of rapid onset of short-lived impairment of neurologic function that resolves spontaneously
- No evidence of structural abnormality to the brain seen on standard neuroimaging
- LOC for no longer than 30 minutes
- GCS of 13 or higher on presentation
- PTA for no longer than 24 hrs

American Congress of Rehabilitation Medicine definition of mTBI

A patient with mild traumatic brain injury is a person who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

1. Any period of loss of consciousness;
2. Any loss of memory for events immediately before or after the accident;
3. Any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or confused); and
4. Focal neurological deficit(s) that may or may not be transient; but where the severity of the injury does not exceed the following:
    - loss of consciousness of approximately 30 minutes or less;
    - after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13–15; and
    - posttraumatic amnesia (PTA) not greater than 24 hours

LOC: loss of consciousness; GCS: Glasgow Coma Scale; PTA: post-traumatic amnesia; mTBI: mild traumatic brain injury

Figure 1. CISG definition of concussion and ACRM definition of mTBI

221x253mm (192 x 192 DPI)

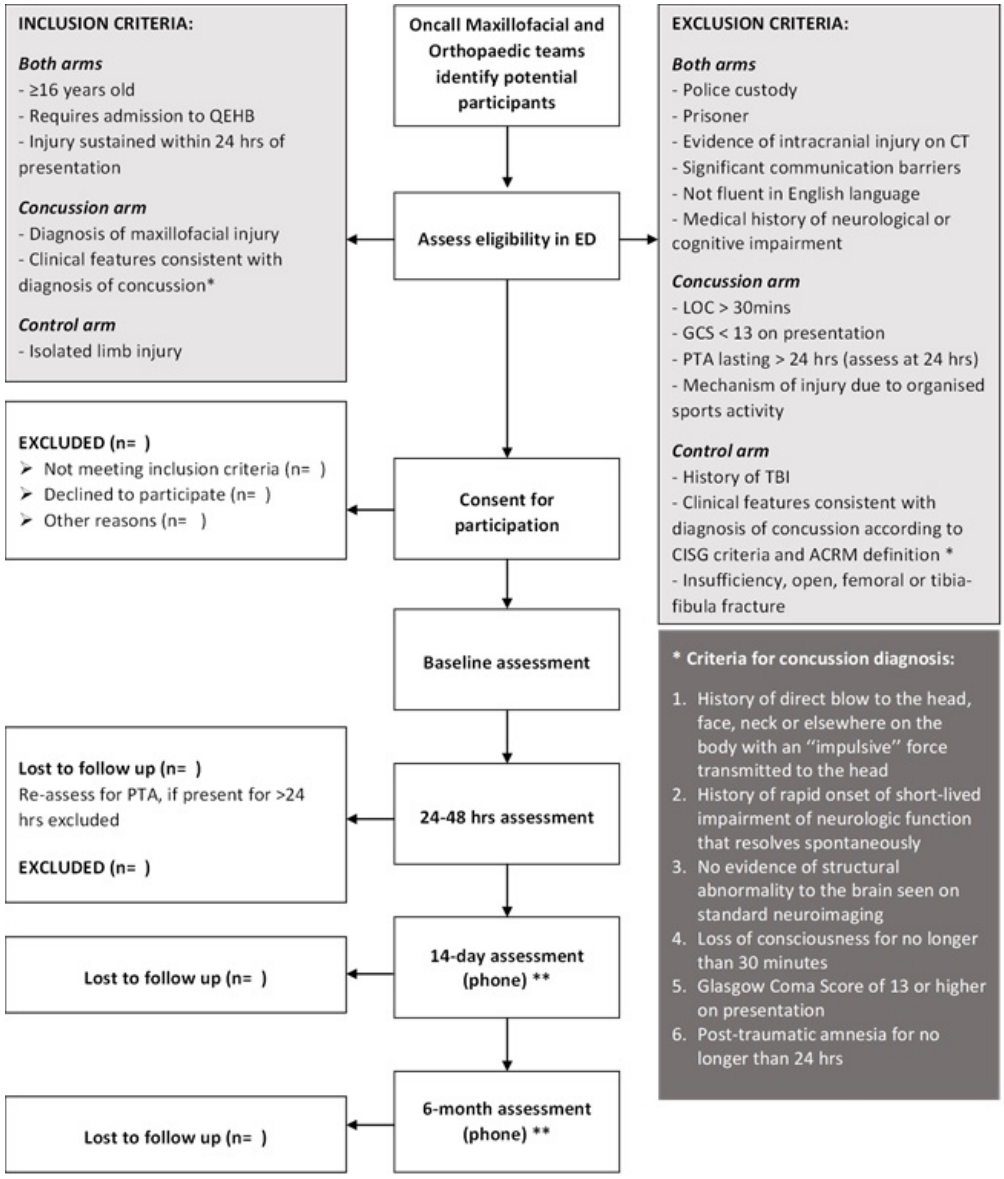

Figure 2. Study protocol flowsheet

86x101mm (192 x 192 DPI)

BMJ Open

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

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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

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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 micro-RNAs (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 (NHS) patients, and whether well-established sports-related concussion (SRC) assessment tools may be translated into the Emergency Department (ED).

Methods and analysis:

CONTACTS 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 version 5 (SCAT5), the Immediate Post-Concussive Assessment and Cognitive Test (ImPACT), and the ImPACT Quick. Follow-up will be at 24-48 hours in-hospital and remotely via telephone and email at14 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, those suffering from mental health conditions and concurrent intoxication) are to be included, to improve the translation into clinical practice
- COVID may limit the amount of time patients are in ED 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". (1) Signs and symptoms are nonspecific 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. (1, 2)

Each year 1.4 million people present to the Emergency Department (ED) in England and Wales with traumatic brain injury (TBI). (3) Since 90% of TBI cases are classified as mild in severity (4) and have an estimated lifetime cost of $5,299, (5) 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. (1) Two such widely accepted tools include the paper-based Sports Concussion Assessment Tool 5th edition (SCAT5) (6) and the computerised neurocognitive Immediate Post-Concussive Assessment and Cognitive Test (ImPACT). (7) 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 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; the “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 (AUC 0.91, 95% CI 0.81 to 1) and 36–48 hours later (AUC 0.94, 95% CI 0.86 to 1). (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 a far greater variation in age, and physical and cognitive baseline characteristics of patients presenting with a head injury.

Sports Concussion Assessment Tool 5th edition (SCAT5)

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 5th 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 in patients 13 years or older and should take no less than 10 minutes to perform. The diagnostic utility of the SCAT decreases after 3–5 days and has limited utility in tracking the recovery of patients. (6) The assessment should be conducted by healthcare professionals only and is not designed to be a standalone 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 (12) 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 (SAC) score.

Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

The ImPACT is a computer-based neurocognitive assessment widely used of professional sports. (7) The ImPACT should be administered by a healthcare professional and is validated for patients aged 12-59 years. The test should take 20-25 minutes to administer and considers several different

assessment domains. As with the SCAT5, the ImPACT is not designed to be used as a standalone 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.

Table 1. ImPACT composite score calculations

ImPACT composite score	Calculation
Verbal memory	Average of these scores: • Word Memory total percent correct (immediate + delay) / 2 • Symbol Match (hidden symbols)/9*100 • Three letters Total letters correct
Visual memory	Average of the following scores: • X's and 0's-total correct (interference) total/4 • Design memory-total percent correct (immediate + delay) / 2
Reaction time	Average of these scores: • X's and 0's average correct RT • Symbol Match average correct RT/3 • Colour Match average correct RT
Processing speed	Average of the following scores: • X's and 0's-total correct (interference) total/4 • Three letters-average counted correctly*3
Impulse control	Sum of the following scores: • X's and 0's-total incorrect –interference • Colour match total commissions

This requires a pre-injury assessment to which post-concussion scores are compared. The program calculates a reliable change index (RCI) score and where this exceeds the expected range in variation, identifies it as abnormal. (7) The ImPACT Quick programme was designed for use at the pitch side and

to aid in removal-from-play decisions. Rather than relying on a pre-test 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 three of the sixty-nine 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 were found between groups at any of the time points. By comparison, an Australian study assessing 79 concussed patients to 86 trauma control patients in the ED found significant differences in all 5 composite domain scores. (17)

RATIONALE

Previous work suggests that concussion remains underdiagnosed in the ED (18, 19) and patients may not be followed up adequately in clinical practice. (20) 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. (18) 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 (NICE) 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

CONTACTS 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 1, feasibility study followed by a phase 2, substantive study if progression criteria are met. Both phases will take place at the Queen Elizabeth Hospital Birmingham (QEHB) as a single-centre study. Participants will be followed up for 6 months post recruitment. Phase 1 commenced on 21/07/2021 and the planned end date for recruitment to all study phases is 01/10/2023.

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 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 CISG 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 (3) 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.

Table 2. Summary of eligibility criteria for the CONTACTS study

Cohort	Inclusion	Exclusion
Both	≥16 years old	Police custody
	Requires admission to QEHB	Prisoner
	Injury sustained within 24 hrs of presentation	Evidence of intracranial injury on CT (if performed as part of standard clinical care)
		Significant communication barriers
		Not fluent in the English language
		Prior medical history of neurological or cognitive impairment
Concussed	Diagnosis of maxillofacial injury	LOC > 30mins
	Clinical features consistent with a diagnosis of concussion: - History of direct blow to the head, face, neck, or elsewhere on the body with an ''impulsive'' force transmitted to the head - History of rapid onset of short-lived impairment of neurologic function that resolves spontaneously - No evidence of structural abnormality to the brain seen on standard neuroimaging - LOC ≤ 30 minutes - GCS ≥ 13 on presentation - PTA ≤ 24 hrs	GCS < 13 on presentation
		PTA lasting > 24 hrs (assess at 24 hrs)
		Mechanism of injury due to organised sports activity
Control	Diagnosis of isolated limb injury	History of TBI
		Clinical features consistent with a diagnosis of concussion according to CISG criteria and ACRM definition
		Insufficiency, open, femoral, or tibia-fibula fracture

LOC (loss of consciousness), GCS (Glasgow Coma Scale), PTA (post-traumatic amnesia)

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 to 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 (AIS) severity codes to concussion and facial injuries. (21) Isolated lower limb injuries requiring admission will also receive similar management to 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 (NIHR SRMRC) 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 of members ranges from mid-twenties 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 1) aims to recruit 30 patients within 6 months. Phase 1 will end after 6 months or following the 14-day post-injury time-point of participant number 30—whichever comes sooner. Following the completion of phase 1, 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 2

Amber: remediable issues that require attention before progressing to phase 2

Green: no concerning issues that threaten the success of the trial; continue to phase 2 without substantial amendment (minor amendments may be required).

Progression criteria are listed below:

1. The target recruitment rate is 5 participants per month. If fewer than 70% of the target recruitment number (21 patients) have been recruited by month 6 of phase 1 without identifiable and correctable cause it would not be feasible to progress to phase 2.
2. Following phase 1, if the loss to follow up at the 24-48 hrs and 14-day time-points exceed 30% in either arm without identifiable and correctable cause, it would not be feasible to progress to phase 2 without substantial amendment nts to 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 computerised tomography (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 CISG definition of concussion (1) and the American Congress of Rehabilitation Medicine (ACRM) (2) 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 concussion, this may not be possible.

The process for obtaining consent in patients lacking capacity is outlined below:

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 written agreement from a nominated consultee. If a personal consultee becomes available, then the study will be discussed with them, and written agreement 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 participant choose to withhold consent or written agreement, then the participant will be withdrawn from the study. An agreement with the participant or 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

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.

Nominated consultee definition

An independent healthcare professional (IHP) 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 (CRF). Tables 3 and 4 contain summaries of relevant baseline data and study assessment to be collected at timepoints in the ED, at 24-28hours, 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 the real-life clinical environment to provide a true reflection of the translatability of any study results.

Table 3. Baseline data to be collected in the Emergency Department

Standard of care	Patient demography
	Past medical history (including co-morbidities and medications)
	Injury related events (time of injury, mechanism of injury, 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
Study related sample	Saliva sample

Table 4. Summary of study assessments at 24-48h, 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)

Qualitative assessment

A qualitative telephone interview will be conducted at 6 months following enrolment. As suggested by the TAG PPIE 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 semi-structured" interviews on an individual basis. These are interviews organised around a set of predetermined open-ended questions, with other questions generated from subsequent dialogue between interviewer and interviewee. (22) 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 ten 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 degrees freezer. miRNA profile will be analysed using standard qPCR technique. Once the study has been completed all samples will be destroyed.

Sample size calculation

As phase 1 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. (23, 24) Hence, phase 1 of this study will aim to recruit 30 patients to estimate the mean and SD of the 7 SCAT5 domain scores and 3 composite ImPACT Quick domain scores in the ED. This will also allow the recruitment and retention rates to be estimated with 95% confidence interval maximum widths of 27% and 35% respectively.

The sample size for phase 2 will be calculated based on the observed distributions of outcome scores in phase 1.

Statistical analysis plan

The data analysis for phase 1 will be descriptive and mainly focus on confidence interval 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 1 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 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 standard deviations, with differences in means with 95% confidence intervals 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 2 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 1)

The scores in the three ImPACT Quick domains (speed, memory and attention) and 7 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% confidence intervals. Unadjusted models will be used in the event of the adjusted models failing to converge.

Secondary outcome analysis (Phase 2)

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 hazard ratios, 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 (COREQ) 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 University of Birmingham.

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

CONTRIBUTIORSHIP

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

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Funding grant awards: not applicable.

COMPETING OF INTERESTS

Prof A Belli and Dr V Di Pietro are members of the research team and shareholders for Marker Diagnostics ltd, the company providing the funding for the salivary miRNA tests.

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FIGURE LEGENDS

Figure 1. CISG definition of concussion and ACRM definition of mTBI

Figure 2. Study protocol flowsheet

Concussion in Sport Group definition of concussion

- History of direct blow to the head, face, neck or elsewhere on the body with an ''impulsive'' force transmitted to the head
- History of rapid onset of short-lived impairment of neurologic function that resolves spontaneously
- No evidence of structural abnormality to the brain seen on standard neuroimaging
- LOC for no longer than 30 minutes
- GCS of 13 or higher on presentation
- PTA for no longer than 24 hrs

American Congress of Rehabilitation Medicine definition of mTBI

A patient with mild traumatic brain injury is a person who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

1. Any period of loss of consciousness;
2. Any loss of memory for events immediately before or after the accident;
3. Any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or confused); and
4. Focal neurological deficit(s) that may or may not be transient; but where the severity of the injury does not exceed the following:
    - loss of consciousness of approximately 30 minutes or less;
    - after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13–15; and
    - posttraumatic amnesia (PTA) not greater than 24 hours

LOC: loss of consciousness; GCS: Glasgow Coma Scale; PTA: post-traumatic amnesia; mTBI: mild traumatic brain injury

Figure 1. CISG definition of concussion and ACRM definition of mTBI

221x253mm (192 x 192 DPI)

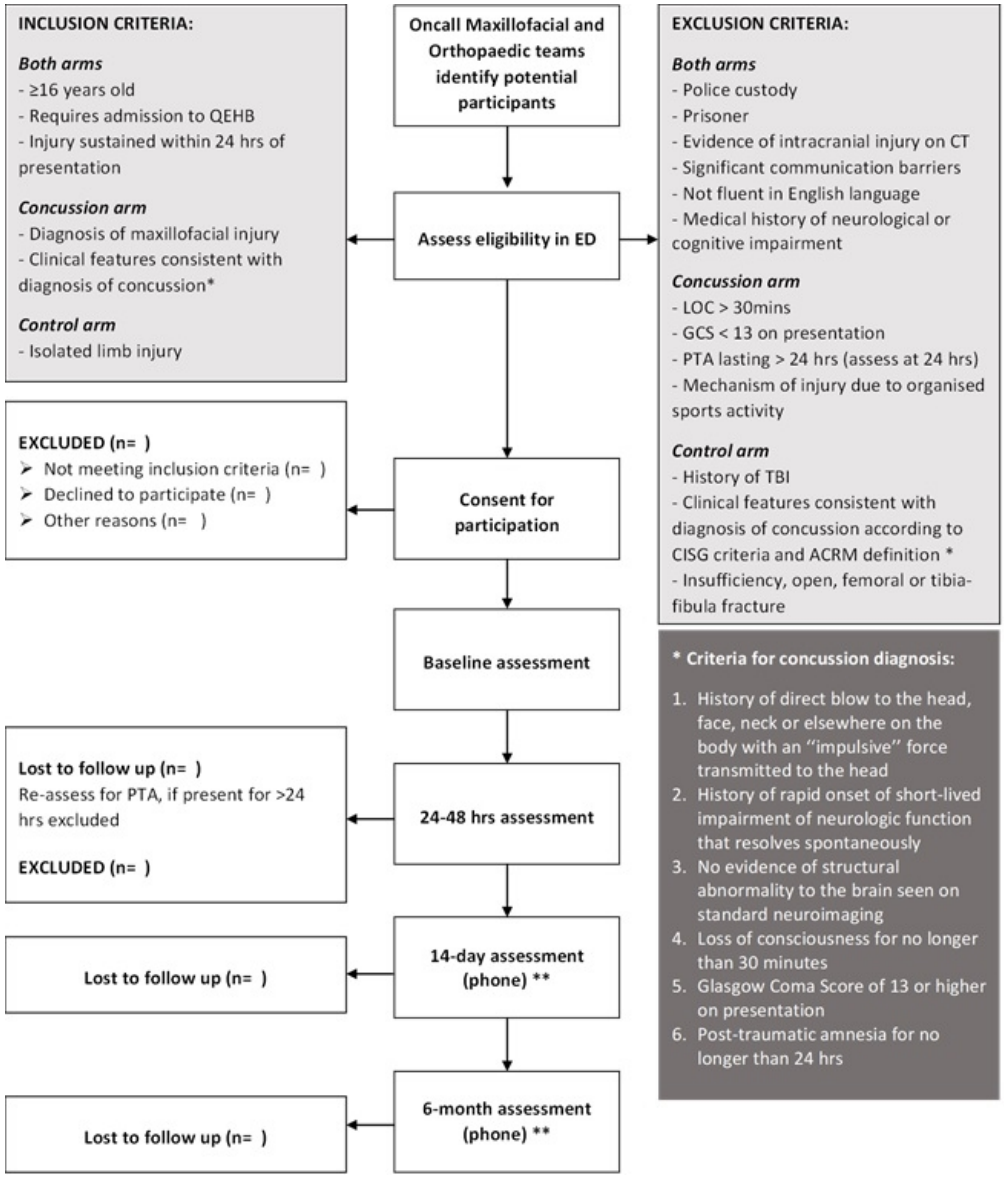

Figure 2. Study protocol flowsheet

86x101mm (192 x 192 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Line location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	33-58
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	77-187
Objectives	3	State specific objectives, including any prespecified hypotheses	39-42
Methods			
Study design	4	Present key elements of study design early in the paper	191-259
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	197-200
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	207-228
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	308-330
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	124-167 308-330
Bias	9	Describe any efforts to address potential sources of bias	224-228
Study size	10	Explain how the study size was arrived at	342-350
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	376-390
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	352-390
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a protocol
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a protocol
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n/a protocol
		(b) Give reasons for non-participation at each stage	n/a protocol
		(c) Consider use of a flow diagram	n/a protocol
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	n/a protocol
		(b) Indicate number of participants with missing data for each variable of interest	n/a protocol

		(c) Summarise follow-up time (eg, average and total amount)	n/a protocol
Outcome data	15*	Report numbers of outcome events or summary measures over time	n/a protocol
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a protocol
		(*b*) Report category boundaries when continuous variables were categorized	n/a protocol
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a protocol
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a protocol
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a protocol
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	62-72
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	n/a protocol
Generalisability	21	Discuss the generalisability (external validity) of the study results	n/a protocol
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	423-426

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.