Study Protocol

Delivery of digital cognitive behavioural therapy following concussion: HeadOn Feasibility Study

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CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SOP	Standard Operating Procedure
ED	Emergency department
CBT	Cognitive Behavioural Therapy
EMERGE	Emergency Medicine Research Group Edinburgh
USA	United States of America
PHQ9	Patient Health Questionnaire 9
GOSE	Glasgow Outcome Scale Extended
EMA	Ecological Momentary Assessment

INTRODUCTION

1.1 BACKGROUND

Concussion is defined as a traumatically induced physiological disruption of brain function. This can occur in a wide range of circumstances from sports and military related injuries, assault, road-traffic accidents and falls. Reliable quantification of the public health burden of concussion is challenging because many patients do not present to healthcare services after sustaining one. However, it is clear that concussion and mild traumatic brain injury is the commonest reason for the under 65s to be admitted to hospital (Scottish Intercollegiate Guidelines Network, 2013). Estimates place the incidence at 300 people per 100 000 seeking medical attention however this varies internationally reflecting the availability of emergency medical services (Cassidy *et al.*, 2004). This incidence is believed to almost double when patients who do not seek medical attention are taken into account. Concussion does not cause the irreversible brain damage associated with more severe traumatic injuries but, there is growing evidence that patients may suffer from a constellation of physical, emotional and cognitive symptoms after a concussion. There is considerable controversy surrounding the natural history, mechanisms, causality and prognosis of post-concussion symptoms. A prospective cohort study of patients presenting to the emergency department after a concussion found that at 3 months 77% reported at least 1 post-concussion symptom (McMahon *et al.*, 2013). The impact of patients suffering from these symptoms on healthcare services is highlighted in a study by Hartvigsen and colleagues who found that over 90% of patients had sought care from at least one healthcare professional related to their symptoms at each of the 5 assessed time-points during the 1-year follow-up period (Hartvigsen *et al.*, 2014). Concussions also have been found to negatively impact on patients' quality of life and return to work (Emanuelson *et al.*, 2003; Graff *et al.*, 2019). In the NHS there is no coordinated clinical pathway for patients following a concussion.

Despite disagreement on the exact aetiology of post-concussion symptoms, there is a view that a complex interplay between biological, social and psychological factors drive the observed clinical phenotype. Therefore psychological interventions have been assessed to determine their value as therapies. Cognitive Behavioural Therapy (CBT) is a psychological intervention that uses personal coping strategies focusing on the interplay between behaviours, thoughts and feelings. There is a strong evidence base on the effectiveness of CBT in a range of mental health problems (Hofmann *et al.*, 2012). A systematic review found that CBT has been assessed in the context of concussion in 3 randomized controlled trials and concluded that it is likely to be effective in the treatment of post-concussion symptoms (Al Sayegh *et al.*, 2010). However, providing face-to-face therapy is highly labour intensive and there are considerable logistical and economic hurdles in delivering CBT for this patient cohort. Coupled to this, some patients do not wish to have face-to-face therapy sessions due to perceived stigma of talking therapies. Due to these difficulties, there have been efforts to use technology platforms as a means to overcome these barriers. One major success is the company Sleepio which has developed an automated CBT programme for patients with chronic insomnia. A clinical trial of Sleepio demonstrated that it improved sleep and daytime functioning (Espie *et al.*, 2012). Similarly, a systematic review of internet delivered CBT for anxiety and depression concluded that it was a promising alternative to face-to-face therapy (Ebert *et al.*, 2015). CBT therefore has the potential to be effectively delivered digitally and provide a scalable alternative to traditional CBT in the context of concussion.

1.2 RATIONALE FOR STUDY

Concussion is common and patients can go on to suffer with a constellation of symptoms which impacts their functional outcome and quality of life (McMahon *et al.*, 2013). Patient provision with information about their concussion and subsequent follow-up was highly variable in a prospective study in the USA (Seabury *et al.*, 2018). This is also the case with psychological therapies despite the fact there is evidence that CBT can help patients manage their symptoms after a concussion (Al Sayegh *et al.*, 2010).

We have developed HeadOn - a web application that delivers a CBT programme to patients following concussion. The application takes the patient through a 5-stage programme including: (i) understanding post-concussion symptoms; (ii) sleep after a concussion; (iii) lifestyle habits and exercise; (iv) managing negative thought patterns and (v) returning to baseline. The programme is delivered through a combination of weekly tasks (such as completing symptom diary, setting exercise goals and setting up a sleep time routine), audio/video media and reading material.

In this study, we would like to examine the feasibility of digitally delivering a course of CBT to patients following concussion. We hypothesise that patients will find it an acceptable and useful form of treatment. We plan on determining recruitment rates to guide future controlled trials.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

Our primary objective is to determine the following regarding the digital delivery of CBT to patients following concussion:

- Compliance of participants with a digital CBT program
- Usability of a digital CBT program as a form of therapy

2.1.2 Secondary Objectives

Our secondary objectives are:

- Determining functional outcome after the HeadOn program
- Determining the temporal profile of post-concussion symptoms, sleep disturbance and mood during the study period
- Identifying return to work rates
- Recruitment rates of patients presenting to a single emergency department

2.2 ENDPOINTS

2.2.1 Primary Endpoint

1) Participant compliance with CBT program

Data inputted into the digital CBT program will be used as surrogate marker of participant compliance. During each stage of the program participants are required to input data as part of the CBT tasks. Participants will be divided into the following three groups: *Fully compliant:* participants who input data into the program during all five stages; *Partially compliant*: participants who input data but not during all five stages; *Non-compliant*: participants who do not enter any data into the program

2) mHealth App Usability Questionnaire

2.2.2 Secondary Endpoints

1) Post-concussion symptom burden measured using the Rivermead post-concussion questionnaire
2) Mood measured using the PHQ9 questionnaire
3) Quality of sleep measured using the Pittsburgh Sleep Quality Index
4) Functional status measured by Glasgow Outcome Score Extended
5) Healthcare utility questionnaire
6) Time to return to work
7) Willingness to be randomised in future randomised trials
8) Patient recruitment rates

3 STUDY DESIGN

The HeadOn feasibility study is a prospective feasibility study of patients presenting to the Edinburgh Royal Infirmary and St John's Hospital Emergency Departments (ED) **(Figure 1)**. Patients will be identified from the ED. Potentially eligible patients will be contacted by a member of the Emergency Medicine Research Group Edinburgh (EMERGE) research team and their consent will be sought for participation. Those not recruited at presentation to the ED will be contacted by telephone, text or email within two weeks of their concussion date to seek their participation in the study, again by a member of the EMERGE research team. After consenting, the participant will be taken through the registration process for the HeadOn program. For patients who are contacted after discharge they will be taken through registration process over the telephone or if preferable will be able to return to the ED to go over the process.

At registration the participant will be invited to complete a series of patient reported measures including the Rivermead post-concussion questionnaire, Pittsburgh Sleep Quality Index, PHQ9 questionnaire and FAST alcohol questionnaire within the HeadOn program. Alongside this, a series of researcher-led anonymised data points will be collected in a separate specially designed database including demographics, date of concussion, neurological and imaging findings which will all be collected from the medical notes and imaging reports. The HeadOn program runs for five weeks following which the participant will be invited to complete the same set of outcome measures. Alongside this, all the participant will be contacted (via telephone, text or email) by a member of the research team at week 5 to complete a further five measurements: Glasgow Outcome Score Extended, mHealth App Usability questionnaire, time to return to work and a healthcare utility questionnaire. Interested participants will be invited back within two months of enrolling in the study for a more detailed qualitative interviews about HeadOn. The study will recruit for a period of 6-months or up to 100 participants.

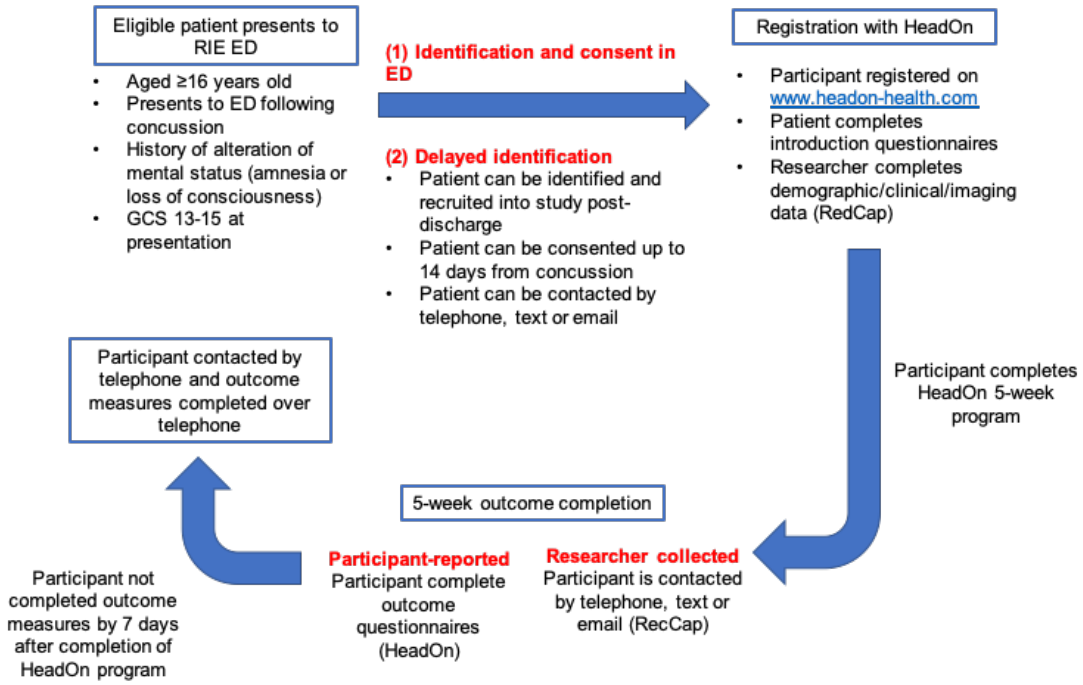

Figure 1: Schematic of HeadOn study design

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

The study aims to recruit over a 6-month period at the Royal Infirmary of Edinburgh and St John's Hospital ED with the aim to recruit 100 participants.

4.2 INCLUSION CRITERIA

- Patients aged 16 years and older (no upper age limit)
- Presenting to the ED with a concussion
- Concussion defined as a traumatically induced alteration of mental status (either defined as loss of consciousness and/or amnesia)
- Patient is Glasgow Coma Scale score of 13-15 on initial presentation to the ED
- Patient needs to be able to start using HeadOn within 14 days of their head injury

4.3 EXCLUSION CRITERIA

- Patients aged under 16 years old
- Patients requiring surgical management of their cranial injury
- Significant other associated injuries requiring hospitalisation (spinal injury, fractures, abdominal, cardiothoracic or vascular injuries)
- Does not have capacity to give consent
- Non-English speakers
- Patient in police custody or in prison

4.4 CO-ENROLMENT

Co-enrolment will be permitted with any other study provided it is not expected to place an undue burden upon participants and their families, and will not compromise the primary end-point of either trial. Co-enrolment will only be permitted with agreement of the Chief Investigators of both studies. A written co-enrolment agreement will not be sought for co-enrolment with this study.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Patients will be identified in the ED. The EMERGE team, where it is locally agreed that they are part of the clinical care team, will identify patients using triage information and clinical or electronic records in the ED at presentation or through screening of admission logs. In this case, it is anticipated they would identify patients and make the first approach. Any member of the clinical team who has received general and trial specific training and is on the delegation log may also identify patients in this way.

Patients with concussion do not typically have long stays in ED and can be discharged after a few hours. Those patients that are not approached at admission or not recruited at presentation to the ED will be identified through ED admission logs by a member of the EMERGE team and will be contacted within two week from the date of their concussion to seek their participation in the study by a suitably trained member of the research team.

5.2 CONSENTING PARTICIPANTS

Potentially eligible patients within the ED will be screened by the EMERGE team and approached and verbal consent gained on whether they would be interested to participate by a suitably trained member of the research team. Following this, the patient will be provided with a participant information leaflet (paper or digital). Potential participants will be recruited to the study within the four hour management window in ED. If the patient requires more time to decide

they can express an interest to participate after discharge from ED up to 14 days from the date of their concussion. Those interested to take part in the study will be consented by a member of the research team using the RedCap e-consent function which will be linked through the HeadOn website (www.headon-health.com/research).

Patients that are discharged before they agree to participate in the study or are identified post-discharge can be enrolled in the study by a suitably trained member of the research team up to 14 days from the date of their concussion. Initially patients will be contacted to see if they are interested in receiving information about the study. Those that are will be directed to the HeadOn website or sent the material by their preferred means (email/post). If they are interested in participating, the patients will be directed to the HeadOn website to be consented using the RedCap e-consent function.

5.2.1 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. The participant will have the option of withdrawal from all aspects of the study but continued use of data collected up to that point. To safeguard rights, the minimum personally identifiable information possible will be collected.

6. DATA COLLECTION

Data will be collected at four points during the study period: at baseline, during the HeadOn program, at the final 5-week follow-up and during a voluntary qualitative interview. Two forms of data will be collected: patient-reported and researcher collected.

At baseline, participants will complete four patient questionnaires within the HeadOn program (Rivermead postconcussion, PHQ9, Pittsburgh Sleep Quality and the FAST alcohol screen). Researchers will also capture demographic, clinical and imaging findings data taken from participants notes and investigation finding reports. During the HeadOn program, participants will undergo a series of ecological momentary assessments (EMAs) aimed at capturing information about their symptoms, mood, thoughts about their concussion and behaviour **(Appendix)**. This includes a symptom and mood diary which will be delivered daily. Alongside this, a series of other EMAs are delivered to the participant at different stages of the program **(Figure 2)**: Stage 3 (Alcohol tracker), Stage 4 (Thought diary) and Stage 5 (Goal setting). HeadOn generates automated reminders (by email or notification) to help keep participants engaged. In the final 5-week follow-up of the study, both participant-reported and researcher collected outcome measures will be captured. Participants will complete the following questionnaires digitally through the HeadOn program: Rivermead postconcussion, PHQ9, Pittsburgh Sleep Quality and FAST alcohol screen. The participant will also be contacted by a trained member of the HeadOn research team to complete four questionnaires: the mHealth app usability questionnaire, healthcare utility, return to work questionnaire and the Glasgow Outcome Score Extended (GOSE). The participant will also be reminded to complete the week 5 patient-reported questionnaires if they had not already done so. If the participant has not completed these questionnaires by week 6, then they will be contacted again by a member of the research team to complete these questionnaires.

Patients who have consented to take part in qualitative interviews will be contacted (by phone or email) and invited to participate in an in-depth interview with a member of the research team. Any participant who declines to be interviewed will also be offered to provide their feedback in an online survey. Interviews will be conducted over the telephone or videoconference and will last approximately 40-60 minutes **(Appendix)**. Participants will be asked for their views and experiences on the following topics: (1) about their experience of using the intervention (2) when and how they used the intervention (3) how easy or not easy they found the intervention to use (4) likes and dislikes about the intervention (5) the functions were most useful and least useful (6) what changes they would make within the intervention.

The data captured will be kept in two different databases based upon whether it is participant-reported or researcher collected. Researcher collected data will be entered into a specially designed password protected online accessed secure database (RedCap). REDCap is run by the Surgical Informatics research group (The University of Edinburgh) under licence from Vanderbilt University. REDCap was developed specifically around HIPAA-Security guidelines. It is hosted within the University of Edinburgh Virtual Machine architecture which is physically secured. Linux web servers running apache2/php5 host the application. Web browser communication to the server is SSL-encrypted by default. All other ports are firewall protected. Data is stored in MySQL databases on a separate server. This server is behind a firewall and can only be accessed from the IP address of the web server. An SSL tunnel encrypts communication between the web and databases servers. File upload is secured between servers using the WebDAV protocol with SSL. "At rest" encryption is in place on the database server. Daily back-ups are made of both servers and stored for four weeks prior to being deleted. Operating security updates are installed automatically. Antivirus software runs to a scheduled protocol on the web server. User passwords are managed directly. Accounts are disabled after 5 failed login attempts. Users are auto logged out after 30 mins of no activity. Users are forced to change password after 42 days. Password strength: AT LEAST 9 CHARACTERS IN LENGTH and must consist of AT LEAST one lower-case letter, one upper-case letter, and one number. Daily audit tracking of users is in place with removal of unused user accounts. Participants who consent using the RedCap e-consent function will enter their

name and signature into the system as part of the consent process. Identifiable electronic information will be kept in a separate database on an NHS server, which will not be accessible outside the immediate research team. These data will be linked by study number to the anonymised research database and will be stored on a secure, password protected location on the local hospital computer drive and only accessible to relevant staff. Researcher collected data will be entered directly into the database using the participant's unique study number.

Patient-reported data will be captured through the HeadOn digital platform (www.headon-health.com) which is hosted on the Microsoft Azure cloud computing service which meets industry standard data protection protocols. As part of the registration process, the patient will input their email address, name and study number into the system. Qualitative interviews will be conducted over the telephone and recorded using a digital voice recorder that generates encrypted audio files. These files will be transcribed by Christine d'Offay (Edinburgh University MSc student) and kept on the Edinburgh University network. They will be pseudo-annonymised and linked to participant through their research number.

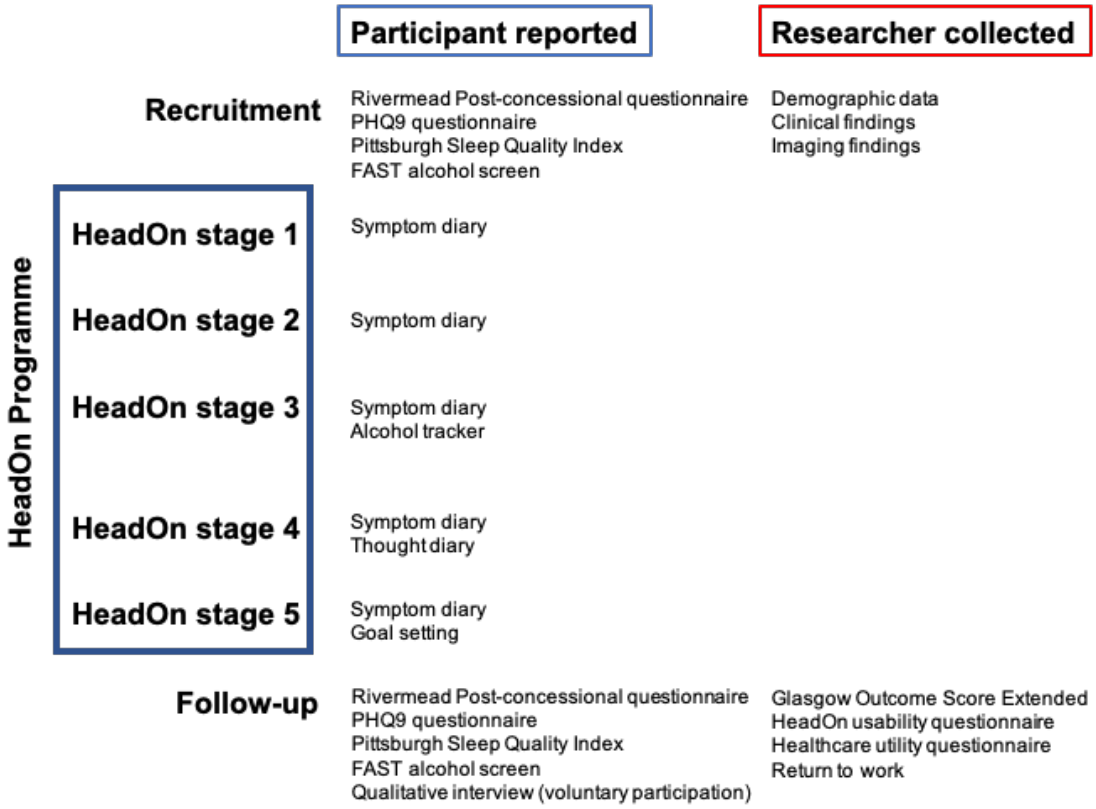

Figure 2: Flow chart demonstrating patient reported and researched collected data collected at different time points.

	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	$-t_1$	0	w_1	w_2	w_3	w_4	w_5	t_x
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTION:								
HeadOn program			←	—	—	—	→	
ASSESSMENTS:								
Baseline variables	X	X						
Researcher collected data		X						X
Patient reported data		X	X	X	X	X	X	X
Qualitative interview								X

Table 1: SPIRIT figure for HeadOn feasibility study

7 DATA MANAGEMENT

7.1 Personal Data

Researcher captured anonymised data will be entered into a specially designed password protected online accessed secure database (RedCap). As detailed above, RedCap complies with stringent data security standards and is hosted within the University of Edinburgh Virtual Machine architecture which is physically secured. Participants will be identified on RedCap by study number alone. Patients who consent using the e-consent RedCap function will enter their name and signature into the system as part of the consent process.

Identifiable electronic information will be kept in a separate database, which will not be accessible outside the immediate research team. These data will be linked by study number to the anonymised research database and will be stored on a secure, password protected location on the local hospital (NHS Lothian) computer drive and only accessible to relevant staff.

Identifiable non-electronic data of the participant will be kept in a locked filing cabinet in a locked local research study office. Computers used to collate the data will have limited access measures via usernames and passwords. A fully anonymised version of the data will be shared on the Edinburgh University DataShare service and made available for 5 years after completion of the study.

Published results will not contain any personal data that could allow identification of individual participants.

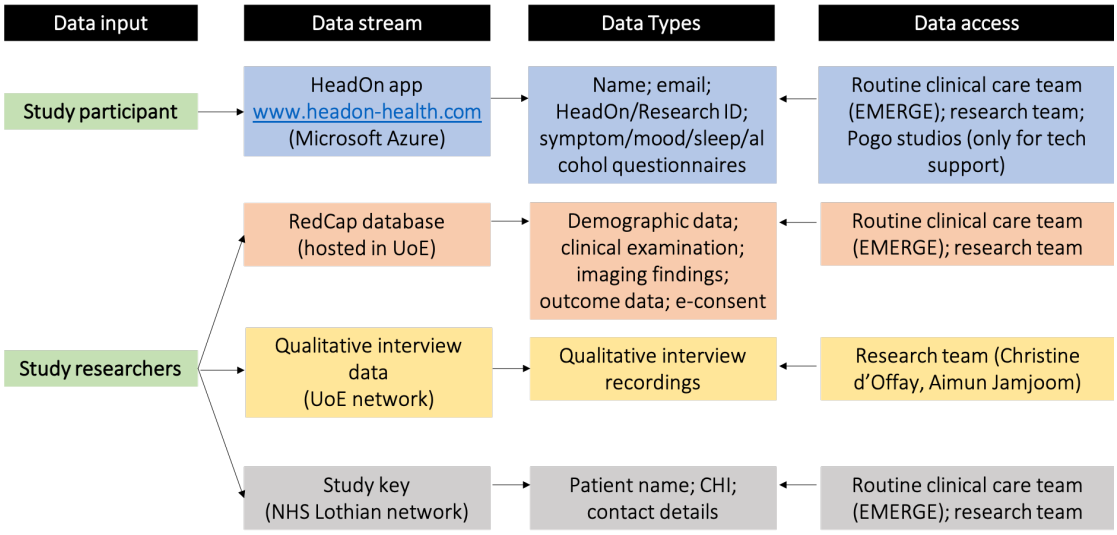

Figure 3: Data flow diagram

Data stream	Data type	Where is database kept?	Who inputs data?	Who has access to data?	Is data anonymous?
HeadOn app www.headon-health.com	Email (mandatory) Name (optional) HeadOn ID Research ID Symptom type/severity Mood Sleep quality Alcohol consumption	Microsoft Azure cloud service	Study participant	Routine clinical care team (EMERGE research nurses) Aimun Jamjoom (PI) Christine d'Offay (MSc student) Pogo Studio Ltd (only if technical issue requiring support)	No. Email and name are identifiable. However, exported data is anonymised with HeadOn / Research ID and file is encrypted
RedCap database	Demographic Clinical examination Imaging findings Outcome data e-consent (name and signature)	Redcap is a medical database platform hosted by Edinburgh University	Routine clinical care team (EMERGE research nurses) Aimun Jamjoom (PI) Christine d'Offay (MSc student)	Routine clinical care team (EMERGE research nurses) Aimun Jamjoom (PI) Christine d'Offay (MSc student)	Yes, linked to identifiable patient data through research ID number
Study key (excel sheet)	Patient name, CHI; contact details; research number; recruitment data	Dataform containing patient name, CHI; contact details and research number which is kept on NHS Lothian computer network	Routine clinical care team (EMERGE research nurses) Aimun Jamjoom (PI) Christine d'Offay (MSc student)	Routine clinical care team (EMERGE research nurses) Aimun Jamjoom (PI) Christine d'Offay (MSc student)	No
Qualitative interview data	Audio recordings of qualitative interviews	Edinburgh university network	Christine d'Offay	Aimun Jamjoom (PI), Christine d'Offay (MSc student)	Yes, only research ID used

Table 2: Data stream details

7.2 Transfer of Data

Data entry will be completed by the local research team and data analysis by the study statistician. Participants enter identifiable data (name/email address) outwith the local NHS region as part of the HeadOn registration process and RedCap e-consent function. Participant identifiable data will be removed from any electronic data being sent for analysis.

7.3 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws.

The Chief Investigator will be responsible for the quality of the data recorded in the electronic CRF on the research database.

All Investigators and study site staff involved with this study will comply with the requirements of the Data Protection Act 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants, representatives of the sponsor and representatives of regulatory authorities.

7.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

From admission data from the Royal Infirmary of Infirmary and St John's Hospital ED, approximately 1000 patients that meet our inclusion criteria present to the hospital every year. Over a 6-month period, there would be approximately 500 eligible patients. Assuming a recruitment rate of ~30% we are aiming to recruit 100 participant during the study period.

8.2 PROPOSED ANALYSES

We plan on conducting the following analyses. The study PI will be performing the analysis:

8.2.1 Patient demographics

We plan on conducting descriptive analyses of patient demographics, clinical findings and imaging reports.

8.2.2 Recruitment rates

In this analysis, we will be calculating the recruitment rate as determined by the number of patients consenting to participate compared to those screened and eligible for recruitment.

8.2.3 Patient compliance

During each stage of the program participants are required to input data as part of the CBT tasks. Participants will be divided into the following three groups:

a) *Fully compliant:* participants who input data into the program during all five stages

b) *Partially compliant*: participants who input data but not during all five stages

c) *Non-compliant*: participants who do not enter any data into the program

We plan to conduct simple descriptive analysis to better understand trends in patient interaction with HeadOn.

8.2.4 Temporal change in secondary outcome measures

A number of secondary outcome measures are examined at both recruitment and at the 5-week follow-up (Rivermead post-concussion questionnaire, PHQ9 questionnaire, Pittsburgh Sleep Quality Index). We plan a descriptive analysis of the temporal changes in the aggregate scores of these measures.

8.2.5 Functional outcome

The Glasgow Outcome Scale extended is being used to determine functional outcome in this study. It is an 8-level scale with 8 representing a complete recovery down to 1 which is death. We plan on dichotomising participants to complete recovery (score 8) versus incomplete recovery (<8). Logistic regression will then be used to examine the predictive role of a range of admission data points (demographics, clinical findings (LOC vs no LOC, amnesia vs no amnesia) and admission patient reported measures (Rivermead, PHQ9).

8.2.6 HeadOn symptom diary data

As part of our analysis, we aim to examine the association between data collected in the HeadOn symptom diary and functional outcome. Participants will be dichotomised based on their aggregate scores of the symptom diary. Logistic repression will then be used to examine its predictive relationship with GOSE outcome.

9 ADVERSE EVENTS

This is a low-risk study. Participants found to have a PHQ9 score of >20 will be told of the result and asked if their GP can be informed of the finding to arrange appropriate follow-up and management.

10 OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

10.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written/electronic information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

11.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

11.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

11.2.4 Investigator Documentation

- The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

11.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

11.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study.. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.2 MANAGEMENT OF PROTOCOL NON-COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

12.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

Once the study is completed, patient access to the HeadOn site will be restricted to allow analysis of the data and the integration of any development changes to the program.

12.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. Authorship in any ensuing publications will be conducted as per the International Committee of Medical Journal Editors standards.

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15 APPENDIX

Headaches	0	1	2	3	4
Feelings of Dizziness	0	1	2	3	4
Nausea and/or Vomiting	0	1	2	3	4
Noise Sensitivity, easily upset by loud noise	0	1	2	3	4
Sleep Disturbance	0	1	2	3	4
Fatigue, tiring more easily	0	1	2	3	4
Being Irritable, easily angered	0	1	2	3	4
Feeling Depressed or Tearful	0	1	2	3	4
Feeling Frustrated or Impatient	0	1	2	3	4
Forgetfulness, poor memory	0	1	2	3	4
Poor Concentration	0	1	2	3	4
Taking Longer to Think	0	1	2	3	4
Blurred Vision	0	1	2	3	4
Light Sensitivity, Easily upset by bright light	0	1	2	3	4
Double Vision	0	1	2	3	4
Restlessness	0	1	2	3	4

Appendix I: Rivermead Post-concussion Questionnaire

PATIENT HEALTH QUESTIONNAIRE-9

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING

0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Appendix II: PHQ-9 Questionnaire

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

1. During the past month, when have you usually gone to bed at night?

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

3. During the past month, when have you usually gotten up in the morning?

4. During the past month, how many hours of actual sleep did you get at night? (This maybe different than the number of hours you spend in bed.)

5. During the past month, how often have you had trouble sleeping because you…

(a) Cannot get to sleep within 30 minutes.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(b) Wake up in the middle of the night or early morning.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(c) Have to get up to use the bathroom.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(d) Cannot breathe comfortably.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(e) Cough or snore loudly.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(f) Feel too cold.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(g) Feel too hot.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(h) Had bad dreams.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(i) Have pain.	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

6. During the past month, how would you rate your sleep quality overall?

Very good | Fairly good | Fairly bad | Very bad

7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

Not during the past month | Less than once a week | Once or twice a week | Three or more times a week

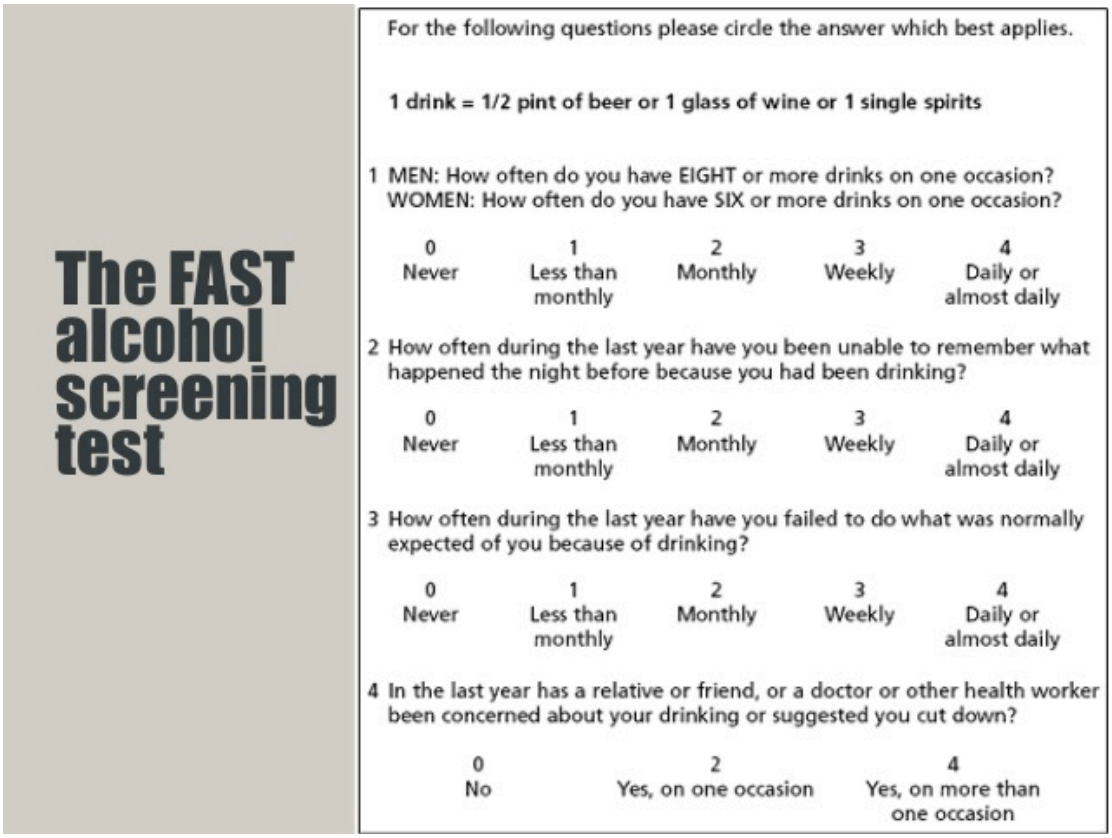
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month | Less than once a week | Once or twice a week | Three or more times a week

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all | Only a very slight problem | Somewhat of a problem | A very big problem

Appendix III: Pittsburgh Sleep Quality Index



The FAST alcohol screening test

For the following questions please circle the answer which best applies.

1 drink = 1/2 pint of beer or 1 glass of wine or 1 single spirits

1 MEN: How often do you have EIGHT or more drinks on one occasion?
WOMEN: How often do you have SIX or more drinks on one occasion?

0	1	2	3	4
Never	Less than monthly	Monthly	Weekly	Daily or almost daily

2 How often during the last year have you been unable to remember what happened the night before because you had been drinking?

0	1	2	3	4
Never	Less than monthly	Monthly	Weekly	Daily or almost daily

3 How often during the last year have you failed to do what was normally expected of you because of drinking?

0	1	2	3	4
Never	Less than monthly	Monthly	Weekly	Daily or almost daily

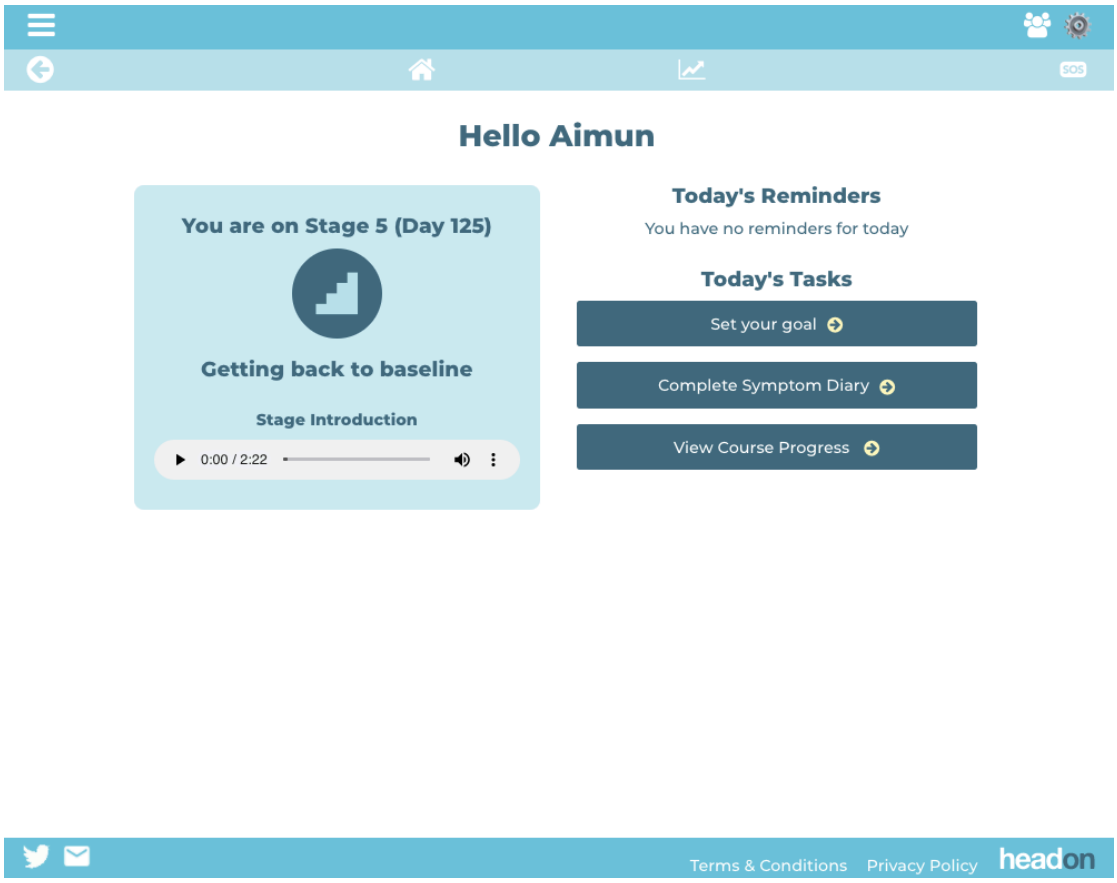
4 In the last year has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?

0	2	4
No	Yes, on one occasion	Yes, on more than one occasion

Appendix IV: FAST alcohol screening test

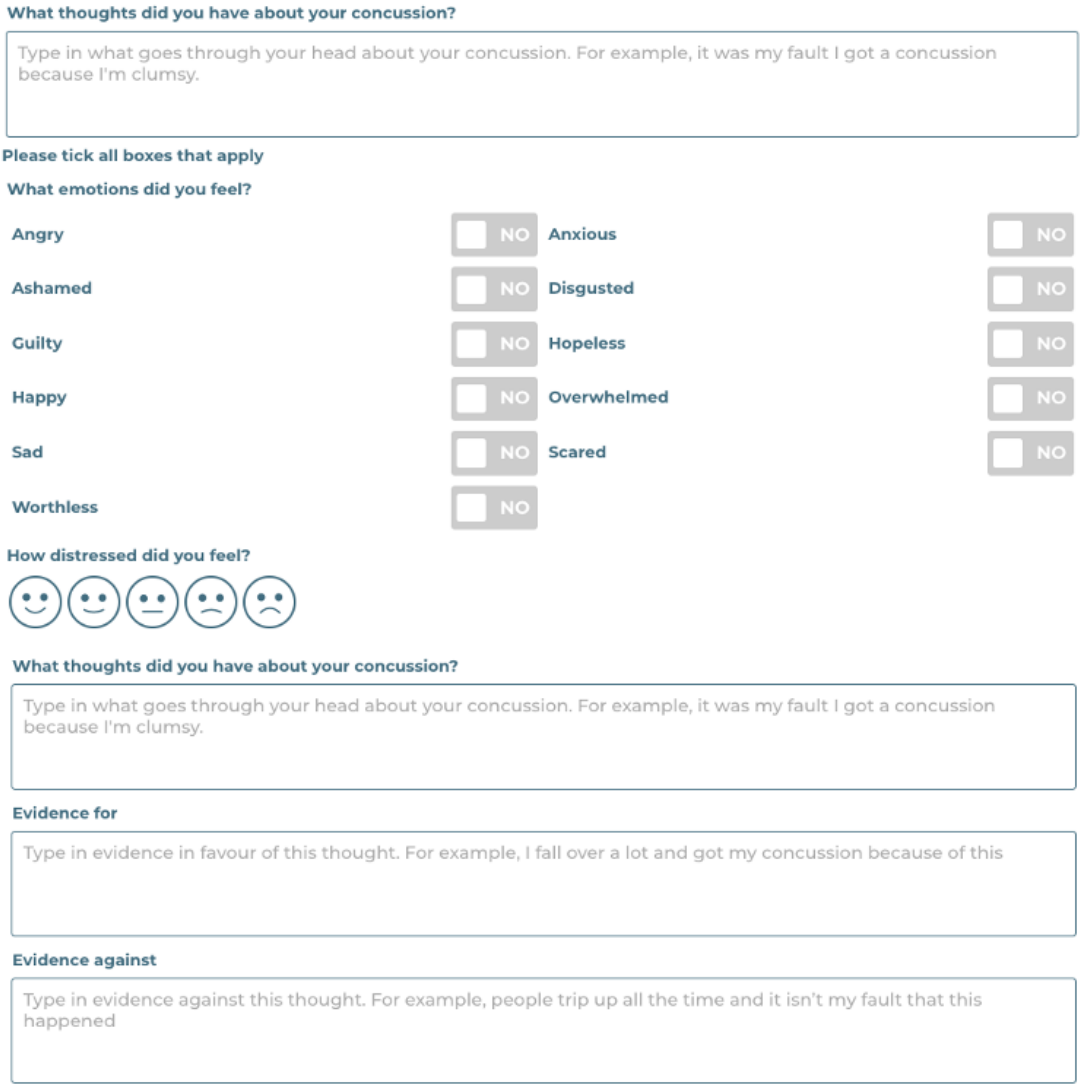
mHealth App Usability Questionnaire							
	Strongly agree						**Strongly disagree**
The app was easy to use	1	2	3	4	5	6	7
It was easy for me to learn to use the app	1	2	3	4	5	6	7
I like the interface of the app	1	2	3	4	5	6	7
The information in the app was well organised, so I could easily find the information I needed	1	2	3	4	5	6	7
I feel comfortable using this app in social settings	1	2	3	4	5	6	7
The amount of time involved in using this app has been fitting for me	1	2	3	4	5	6	7
I would use this app again	1	2	3	4	5	6	7
Overall, I am satisfied with this app	1	2	3	4	5	6	7
Whenever I made a mistake using the app, I could recover easily and quickly	1	2	3	4	5	6	7
This mHealth app provided an acceptable way to receive healthcare services	1	2	3	4	5	6	7
The app adequately acknowledged and provided information to let me know the progress of my actions	1	2	3	4	5	6	7
The navigation was consistent when moving between screens	1	2	3	4	5	6	7
The interface of the app allowed me to use all the functions (such as entering information, responding to reminder, viewing information) offered by the app	1	2	3	4	5	6	7
This app has all the functions and capabilities I expect it to have	1	2	3	4	5	6	7
The app would be useful for my health and well-being	1	2	3	4	5	6	7
The app improved my access to healthcare services	1	2	3	4	5	6	7
The app helped me manage my health effectively	1	2	3	4	5	6	7
The app made it convenient for me to communicate with my healthcare provider	1	2	3	4	5	6	7
Using the app, I had many more opportunities to interact with my health care provider	1	2	3	4	5	6	7
I felt confident that any information I sent to my provider using this app would be received	1	2	3	4	5	6	7
I felt comfortable communicating with my healthcare provider using the app	1	2	3	4	5	6	7

Appendix VI: mHealth App Usability Questionnaire (Zhou *et al.*, 2019)



Appendix VII: HeadOn homepage showing reminder/task sections alongside the weekly audio which introduces the stage.

Appendix VIII: HeadOn Symptom diary



Appendix IX: HeadOn thought monitor

Interview Guide

Participants will be initially asked about their concussion and or/use of health apps. The list of topics asked to participants include;

1. About their experience of using the HeadOn
2. When and how they used the intervention
3. How easy or not easy they found the intervention to use
4. Likes and dislikes about the intervention
5. The functions which were most useful and least useful
6. What changes they would make to improve HeadOn

Appendix X: Qualitative interview schedule overview