STUDY PROTOCOL

Traumatic brain injury related changes in military veterans

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Protocol development and sign off

Protocol Contributors

The following people have contributed to the writing of this protocol:

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Protocol Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

CI Signature Page

This protocol has been approved by:

Study Name:	Traumatic brain injury related changes in military veterans
Protocol Version Number:	Version: _3_.0__
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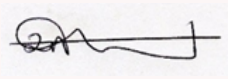
Trial Role:	Chief Investigator
Signature and date:	_____  _____ _11 / _10 _ / _2023_

Sponsor statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

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STUDY SUMMARY

Title

Traumatic brain injury related changes in military veterans

Study Design

Prospective observational pilot study

Objectives

- To evaluate candidate biomarkers in blood and saliva from veterans and non-veterans with traumatic brain injury and correlate these with visual and mental health assessments and patient reported outcome measures.
- To assess mental health status in traumatic brain injured patients and correlate these with changes in patient reported outcomes to assess quality of life over time.
- To relate these changes after traumatic brain injury to understand how quality of life is affected by injury.

Participant Population and Sample Size

Up to 90 subjects

Outcome Measures

- Fluid biomarker levels in blood and saliva including neuronal damage and immune markers.
- Visual function tests including optical coherence tomography, visual field, visual acuity, colour vision, contrast acuity, pupil reactivity, focussing mechanism and eye movement.
- Mental health and quality of life outcomes: social and occupational functioning assessment scale (SOFAS) and self-reported measures such as BIVSS (visual impairments), PHQ-9 (Patient Health Questionnaire; depression), GAD-7 (General Anxiety Disorder), PCL-5 (PTSD checklist for DMS-5), SBQ-R (Suicidal Behaviour Questionnaire Revised), AUDIT (Alcohol Use Disorders Identification Test) and EQ5D5L36 (quality of life).

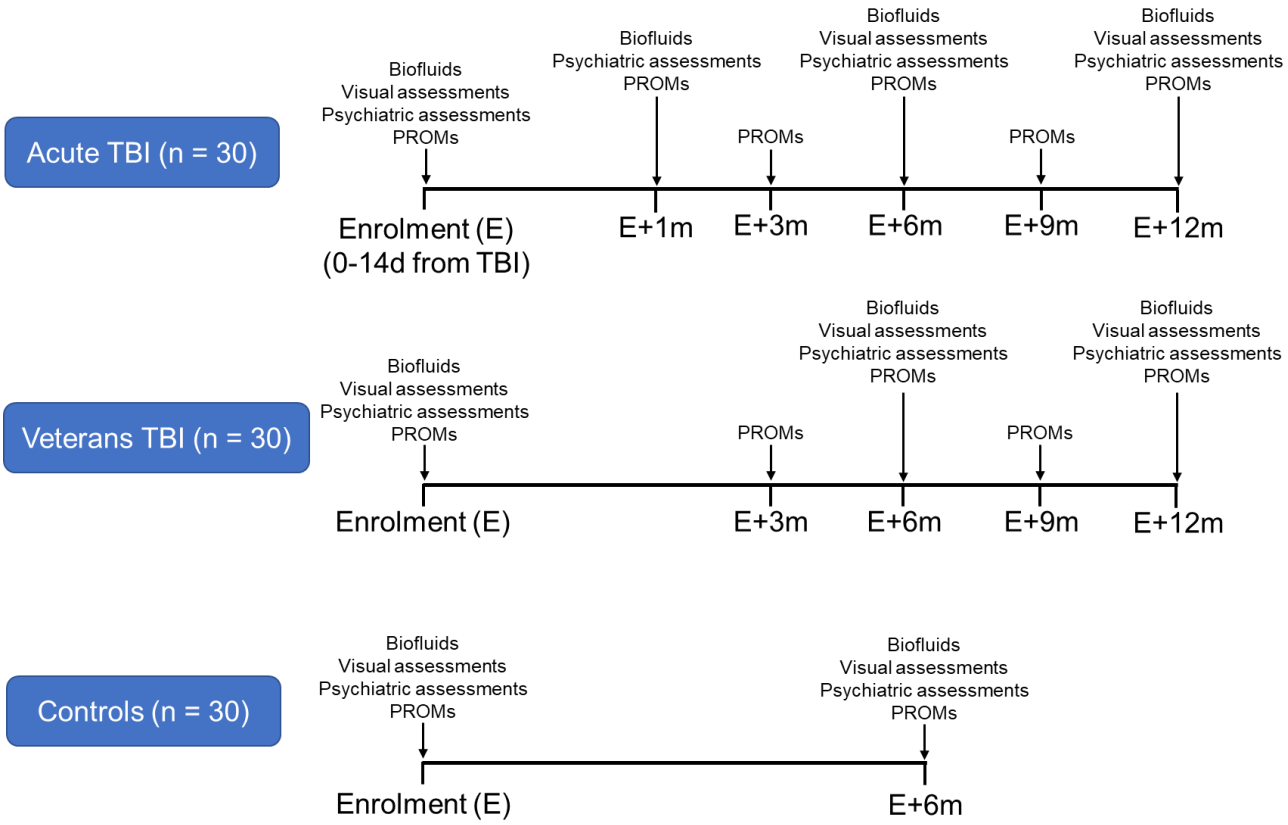
Key Eligibility Criteria

Inpatient or outpatient care after moderate to severe traumatic brain injury

Intervention

None

Trial Schema


Acute TBI (n = 30)
Biofluids
Visual assessments
Psychiatric assessments
PROMs
Enrolment (E)
(0-14d from TBI)
Biofluids
Psychiatric assessments
PROMs
E+1m
PROMs
E+3m
Biofluids
Visual assessments
Psychiatric assessments
PROMs
E+6m
PROMs
E+9m
Biofluids
Visual assessments
Psychiatric assessments
PROMs
E+12m
Veterans TBI (n = 30)
Biofluids
Visual assessments
Psychiatric assessments
PROMs
Enrolment (E)
PROMs
E+3m
Biofluids
Visual assessments
Psychiatric assessments
PROMs
E+6m
PROMs
E+9m
Biofluids
Visual assessments
Psychiatric assessments
PROMs
E+12m
Controls (n = 30)
Biofluids
Visual assessments
Psychiatric assessments
PROMs
Enrolment (E)
Biofluids
Visual assessments
Psychiatric assessments
PROMs
E+6m

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1. Background and Rationale

1.1. Background

Traumatic brain injury (TBI) results in disruption of the normal function of the brain caused by blows, bumps or jolts to the head. These injuries can be penetrating or non-penetrating and cause loss of consciousness, impair cognitive function, alter mental state and cause neurological deficits such as muscle weakness and loss of vision. In the most severe form of TBI, the entirety of the brain is affected by diffuse injury and swelling. Treatment modalities vary extensively based on injury severity, ranging from daily cognitive therapy sessions to radical surgery such as bilateral decompressive craniectomies. Psychiatric disorders occur after both mild and severe TBI[1]. For example, TBI patients may develop depression after damage to the prefrontal grey matter, dorsolateral prefrontal cortex and left basal ganglia[1-5]. Some TBI patients develop obsessive compulsive disorder after damage to the orbitofrontal cortex, caudate nucleus, and anterior cingulate[6-10]. Others develop post-traumatic stress disorder and post-traumatic amnesia[11-13], psychosis[5], and personality changes such as apathy[14] and aggression[15]. Poor mental health therefore exacerbates the burden of living with TBI, with some indication that mental health problems precede other areas of functional decline[15].

Overlap in brain injury and mental health occurs as cognitive, psychological, emotional and behavioural responses originate in the brain, with both brain injury and mental illness occurring after damage to neuronal pathways. TRACK-TBI found that 1 in 5 individuals went on to experience mental health issues after mild TBI[15,16] whilst the rates of completed suicide and the relative risk of suicide post-TBI were almost 3 times higher than the general population[16]. Increasingly, TBI fluid and imaging biomarkers are being used for their diagnostic, prognostic and predictive value, as an aide to clinical decision making. Fluid biomarkers from peripheral blood or cerebrospinal fluid can diagnose and determine the severity of TBI. For example, the fluid biomarkers glial fibrillary acidic protein (GFAP), S100β, tumor necrosis factor-α and myelin basic protein (MBP) associated with TBI severity[17]. Since up to 80% of TBI patients suffer visual disturbances, changes in visual structure and function can be used to diagnose and prognosticate TBI[18,15]. Therefore, **a better understanding of the neuropsychiatric changes post-TBI, aided by our collection of biofluids and visual imaging data in military veterans, could inform a larger study to identify potential preventative treatments after TBI but also inform the disease specific and transdiagnostic discovery bioscience with significant and wider impact.**

1.2. Study Rationale

1.2.1. Justification for participant population

Military personnel are increasingly at risk of TBI during conflicts and especially exposure to blast. Severe TBI is easy to spot but over 80% of TBIs in military personnel are mild TBI (mTBI), which is characterised by short-term loss of consciousness and or altered mental state. Mild TBI has emerged as a signature injury and an important concern in both US and UK military populations, because of the potential for long term negative sequalae. Of military personnel returning from Iraq and/or Afghanistan, up to 40% of military personnel in the US had a mTBI[19], whilst the prevalence in the UK cohort was smaller at around 5%[20] with one report suggesting that neuropsychiatric problems could affect as much as 70% of veterans[21]. However, all severities of TBI are associated with a broad range of subsequent psychiatric and neurological disorders including headache, fatigue, sleep disorder, dizziness, amnesia, information processing slowing, executive dysfunction, depression, anxiety and suicidal behaviour[22]. TBI sustained in combat is also accompanied by posttraumatic stress disorder (PTSD) and bodily trauma, which adds to the difficulty in determination of the relative contribution of each of these factors to eventual outcomes. Biomarkers have the potential to help identify those at risk of poor recovery which would aid deployment of early interventions.

The aim of this investigation is to evaluate candidate fluid biomarkers in blood and saliva from veterans who have suffered a TBI and correlate these with visual assessments, standard clinical assessments of mental health and patient reported outcome measures (PROMs) that assess mental health and quality of life over time. All of the data will be combined to develop a multifaceted algorithm to predict prognosis in veterans and provide pilot data to inform a larger study. The study will also identify biomarkers that can enable rapid decisions as to whether further intervention is required to prevent significant changes to qualify of life in veterans with a TBI and inform rehabilitation strategies to increase optimal management opportunities.

1.2.2. Justification for design

This is a prospective observational pilot study. Following 3 groups of participants, including an acute TBI group, a veterans' group with diagnosed TBI and a control group with no previous episodes of brain injury allows us to: (a) assess the changes in fluid and imaging biomarkers and (b) assess mental health status and quality of life over time. Values obtained from levels of biomarkers and measures for mental health status and quality of life will be subtracted from data in the acute TBI and the veteran group. This will reveal changes over time in acute TBI patients who have suffered a TBI and in veterans with TBI. Comparisons between the acute TBI group and the veteran group will then reveal differences between these two groups and whether one group is more susceptible to worse mental health and quality of life status. Since, we will collect longitudinal data, we may be able to tell how long after a TBI do the reported mental health and quality of life problems occur in acute TBI and veterans with a view to developing therapeutic intervention to delay or treat these problems.

We will compare these with the same biomarkers and assessments in control patients (without any episodes of brain injury). This will help us to understand if there is anything different in TBI patients that may tell us who is likely to go onto to develop mental health problems and poorer quality of life outcomes.

Whilst we will aim to perform all investigations at all time points on all patients, not all patients will be able to devote sufficient time and effort to participate and, as this is an exploratory study, we will not exclude patients where they fail to complete all stages of the assessment.

2. Aims, Objectives and Outcome Measures

2.1. Hypotheses

1) TBI alters the structure of the brain causing the development of mental health conditions with time.
2) TBI-induced changes can be detected using fluid and imaging biomarkers.
3) TBI-induced changes in biomarkers may identify those at risk of poor recovery and the development of mental health conditions affecting the quality of life.
4) Changes in visual structure and function predict mental health and quality of life and associate with TBI-related biomarkers.

2.2. Outcome Measures

Fluid biomarker levels in blood and saliva including neuronal damage and immune markers.[23]

Visual function tests such as visual field, visual acuity, colour vision, contrast acuity, pupil reactivity, focussing mechanism and eye movements.[17,18,24,25]

Mental health and quality of life outcomes: social and occupational functioning assessment scale (SOFAS) and self-reported measures such as BIVSS (visual impairments)[24], PHQ-9 (Patient Health Questionnaire; depression)[26], GAD-7 (General Anxiety Disorder)[27], PCL-5 (PTSD checklist for DMS-5)[28], SBQ-R (Suicidal Behaviour Questionnaire Revised)[28], AUDIT (Alcohol Use Disorders Identification Test)[30] and EQ5D5L[31] (quality of life).

3. Trial Design and Setting

3.1. Study Design

Prospective observational pilot study

3.2. Study Setting

The study is conducted at the Queen Elizabeth Hospital, Birmingham.

4. Eligibility

4.1. Inclusion Criteria for acute TBI group

1. Over the age of 18
2. Must have 2 eyes
3. Not all participants will have capacity to consent (e.g. moderate to severe TBI). For these participants, they will require a personal or nominated consultee.
4. Willing and able or consented by consultees to follow the protocol
5. Moderate or severe head injury requiring admission to the Queen Elizabeth Hospital within the prior 14 days

4.2. Inclusion Criteria for veterans' group

1. Over the age of 18
2. Must have 2 eyes
3. Capacity to consent
4. Willing and able to follow the protocol
5. Moderate or severe head injury requiring admission to a military hospital facility or service personnel with planned departure from the Armed Forces within 6 months.

4.3. Inclusion Criteria for control group

1. Over the age of 18
2. Must have 2 eyes
3. Capacity to consent
4. Willing and able to follow the protocol
5. No prior history of head injury (including mild, moderate or severe traumatic brain injury).

4.4. Exclusion Criteria for all 3 groups

1. Patients under 18 years old.
2. Patients registered as sight-impaired or severely sight-impaired
3. Any known prior pre-existing neuropsychiatric condition: dementia, epilepsy on neuro-epileptic drugs, Parkinson's disease, hereditary neurodegenerative conditions.
4. Any known retinal or optic nerve disorder of either eye.
5. Pregnancy

4.5. Additional Exclusion Criteria for control group only:

1. Patients have not suffered a TBI or head injury.

4.6. Eligibility criteria for personal consultee

1. Knows the incapacitated person well (i.e. friend or family member)

2. Must not have a financial interest in the project
3. Capacity to consent

4.7. Eligibility criteria for nominated consultee

1. Only appointed if no family member or friend is willing or able to act as a consultee
2. Must have no connection with the project
3. Capacity to consent

5. Consent

A member of the clinical care team (e.g. doctor, research nurse or practitioner) at Queen Elizabeth Hospital Birmingham will first identify potential acute TBI and control group participants to ascertain whether they are interested in participating in the study. They will be approached after either head injury for the acute TBI group (i.e. 0-14 days post-injury) or any other injury not involving the head for the control group in the inpatient ward or in clinic (outpatient) or during telephone / virtual follow up.

Veterans will be recruited through existing links with the military and as they are discharged from military care into NHS care. This includes partner site the Defence Medical Rehabilitation Centre in Stanford Hall where the clinical care team will identify suitable participants and obtain full written consent prior to participants visiting the Queen Elizabeth Hospital in Birmingham for blood/saliva collection and all tests. Veteran's will also be recruited through advertisements and direct contact with veterans' charities such as Bravo Victor and Blind Veterans UK.

Once an acute TBI or control patient or a veteran has expressed an interest in participating, and has provided full written consent to the clinical care team, they will be introduced to a member of research team (e.g. post-doctoral research fellows or assistants). A member of the research team will determine by talking to the patient and review of the patient's notes whether or not the patient is suitable to participate in the study. If the patient is not suitable for inclusion in the trial, their data will not be retained.

In addition, veterans who have already been discharged from the military will also be recruited through advertisements and direct contact with veterans' charities such as Bravo Victor and Blind Veterans UK. These patients will contact the research team if interested and a trained member will obtain full written consent prior to determining the suitability of the participant in the study.

For all participants, a full explanation about the study objectives, visits and assessments will be given in detail and a patient information sheet (PIS) will be provided to facilitate this process. Investigator(s) will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the study at any time.

In the event that the patient is unconscious, a relative or next of kin will be sought out by the clinical care team to read the Personal Consultee information sheet and personal consultee declaration form (PersCDF). If they are happy for the patient to be involved in the study, they will be asked to sign the consultee declaration form and witnessed by one of the clinical care or research team. If, after including the patient by the PersCDF, the patient's family member thinks the patient would no longer want to be included in the study, they will be withdrawn. For unconscious patients or patients who regain consciousness but do not have the ability to consent, only blood will be collected over time and other measures such as collection of saliva, eye imaging test, SOFAS and PROs will not be possible.

If the patient regains consciousness and is able to consent, the consultee would be notified and the patient would be offered a separate regained capacity PIS and asked if they are happy to be in the study and sign the study consent form. If they would not like to be in the study, the information already collected will be retained and they will be withdrawn from the rest of the study.

If the patient has no relative or next of kin available, a member of the patient's clinical care team will be asked to read the study protocol and PIS and nominated consultee declaration form (ProfCDF). If they are happy for the patient to be involved in the study, they will be asked to sign the nominated consultee declaration form.

All potential participants will be offered the opportunity to discuss and ask questions about the research with a member of the research team after they were introduced by the clinical care team. If the participant expresses a desire to participate in the study, they will be asked to sign and date the latest version of the Consent Form prior to any investigations being carried out. A member of the research or clinical care team will then sign and date the form. A copy of the Consent Form will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the study, the participant's unique study identification number will be entered on the Informed Consent Form maintained in the ISF.

Details of the informed consent discussions with the clinical care team will be recorded in the participant's medical notes. This will include date of discussion, the name of the study, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received. Where consent is obtained on the same day that the study related assessments start, a note will be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each visit the participant's willingness to continue in the study will be ascertained and documented in the medical notes. In the unlikely event that a patient loses capacity while enrolled in the study, a personal consultee or a nominated consultee will be appointed to decide for the patient. If the patient regains consciousness again, the consultee will be notified, and the patient will be given a regained capacity PIS as above. If they would like to stay in the study, they will be asked to sign the consent form. Throughout the study, the participant will have the opportunity to ask questions about the study. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants and consultees will be given time to consider and reconfirm continuation in the study. The participant's right to withdraw from the study will remain.

If the patient is unable to read the information sheet, then it will be read to them if they are able to understand it. If the patient is unable to understand due to language difficulties, then either a relative of the patient or a translator (where available) would be used to explain the study. If the patient is unable to sign to indicate their consent, then their consent to research may be witnessed and documented on the consent form by a family member or if none are available, by a member of the care team. However, if there was any concern that the patient did not adequately understand the information given to them then they would be excluded from the study. If the patient is unable to sign to indicate their consent, then their consent to research may be witnessed and documented on the consent form by a family member or if none are available, by a member of the care team.

Patients who cannot speak and write English will not be able to complete the neuro-cognitive testing nor the PROMs questionnaires and their participation would therefore be limited to blood and saliva collection and retinal imaging plus testing of visual function. Although this is not ideal as we would prefer to collect data on all assessments, blood biomarkers and visual assessments can still be used in our algorithm to predict outcomes as we will used statistical methods that will be able to deal with missing data for some tests.

6. Trial procedures and assessments

6.1. Summary of assessments

Figure *2. Assessments planned for acute TBI patients*

	TRIAL PERIOD			
	Enrolment	**Initial assessment (may be at enrolment)**	**Post-allocation (monitoring interval clinically determined)**	**Close-out**
TIMEPOINT**	***-t_1***	**Contact 1 (0-14 days post head injury or at enrolment)**	***Contact 2-5 (1, 3, 6 and 9 months after head injury or enrolment)***	***Contact 6 (12 months after head injury)***
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
ASSESSMENTS:				
Collect blood and saliva		X (face to face)	X (1 and 6 months only, face to face)	X (face to face)
Visual function tests (e.g. visual acuity and field tests, optical coherence tomography (OCT), OCT angiography, pupillometry, Email saccadic latency and autorefraction.		X (face to face)	X (1 and 6 months only, face to face)	X (face to face)
Mental health outcomes (social and occupational functioning assessment)		X (face to face and remotely)	X (1 and 6 months only, face to face and remotely)	X (face to face or remotely)
Self-reported measures collected by post (e.g. BIVSS (visual impairment, General anxiety disorder, PTSD, Suicidal behaviour, alcohol use and quality of life		X (all collected remotely)	X (1, 3, 6 and 9 months, all collected remotely)	X (all collected remotely)
Head injury outcome				X

Figure *3. Assessments planned for military veterans group*

	TRIAL PERIOD			
	Enrolment	**Initial assessment (may be at enrolment)**	**Post-allocation (monitoring interval clinically determined)**	**Close-out**
TIMEPOINT**	***-t_1***	**Contact 1 (at enrolment)**	***Contact 2-4 (3, 6 and 9 months enrolment)***	***Contact 5 (12 months after enrolment)***
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
ASSESSMENTS:				
Collect blood and saliva		X (face to face)	X (at 6 months only, face to face)	X (face to face)
Visual function tests (e.g. visual acuity and field tests, optical coherence tomography (OCT), OCT angiography, pupillometry, Email saccadic latency and autorefraction.		X (face to face)	X (at 6 months only, face to face)	X (face to face)
Mental health outcomes (social and occupational functioning assessment)		X (face to face and remotely)	X (at 6 months only, face to face or remotely)	X face to face or remotely)
Self-reported measures collected by post (e.g. BIVSS (visual impairment, General anxiety disorder, PTSD, Suicidal behaviour, alcohol use and quality of life		X (all collected remotely)	X (at 3, 6 and 9 months, all collected remotely)	X (all collected remotely
Head injury outcome				X

Figure *4. Assessments planned for non-head injury control group*

	TRIAL PERIOD			
	Enrolment	**Initial assessment (may be at enrolment)**	**Post-allocation**	
TIMEPOINT**		**Contact 1 (single assessment point)**	***Contact 2 (6 months after enrolment)***	
ENROLMENT:				
Eligibility screen		X		
Informed consent		X		
ASSESSMENTS:				
Collect blood and saliva		X (face to face)	X (face to face)	
Visual function tests (e.g. visual acuity and field tests, optical coherence tomography (OCT), OCT angiography, pupillometry, Email saccadic latency and autorefraction		X (face to face)	X (face to face)	
Mental health outcomes (social and occupational functioning assessment)		X (face to face and remotely)	X (face to face or remotely)	
Self-reported measures collected by post (e.g. BIVSS (visual impairment, General anxiety disorder, PTSD, Suicidal behaviour, alcohol use and quality of life		X (all collected remotely)	X (6 months, all collected remotely)	
Head injury outcome		N/A		

6.2 Schedule of Assessments and Risks

Screening/enrolment

Patients' eligibility and willingness to participate will be assessed as described above in the section on consent.

Clinical assessments (Contact 1-6)

All participants recruited will undergo collection of blood and saliva to detect fluid biomarkers of injury, visual function assessments, mental health status and PROMs. Assessments at the 12 month point will be conducted face to face where possible, but where patients are unable to attend (e.g. have moved away) will be conducted remotely. Study time points for visits 2-6 will allow a 10% variation from stated timings. Face to face visits will therefore be at enrolment, 1 month (acute TBI only), 6 months (all patients) and 12 months (acute TBI and veterans where possible).

Taking blood using a needle is uncomfortable, can cause bruising and bleeding and sometimes fainting. Only trained staff will collect the blood samples to ensure this does not occur. Saliva will be collected in a tube and is not invasive and should not cause any problems.

Visual function tests: visual acuity measurements with normal refractive correction and pinhole where vision is less than logMAR 0 monocularly; colour vision assessed monocularly using Colour Assessment and Diagnosis (CAD); visual field assessed using the SITA Fast 24-2 Humphrey Visual Field-testing algorithm, contrast sensitivity test by monocular reading Pelli-Robson contrast chart or Acuity Plus (on the CAD), pupil assessment using a pupillometer and visual focussing mechanism and ocular motility are assessed using autorefraction and Email saccadic latency assessment respectively. OCT will be used to image the retina and optic nerve head. Dilating drops (tropicamide 0.5%) may be applied where necessary to assist the assessment where this would not interfere with assessment by the neurosurgical team (e.g. when an inpatient on neuro-obs). All visual function assessments and OCT imaging will be carried out at contact points 1 and 3 and where possible at close out (contact 6) when the patient is able to cooperate, although all subjective assessments may not be possible in the acute phase after TBI. Additionally, head injury outcome (i.e. Glasgow outcome scale (daily living assessment by a physician); Mayo-Portland Adaptability Inventory (physical and daily living assessment by a physician) will be assessed at the final visit as part of routine care. There are no risks associated with these tests as they are an assessment of patient's abilities by a physician.

We will use eye drops as per standard care to dilate patient eyes, as is routine. This may mean that patient eyes will be more sensitive to light and can take up to 6 hours to become normal. We will recommend the use of sunglasses to minimise the impact of light to patient eyes. We will also recommend that patients do not drive and that someone accompanies them. We will refund travel expenses.

Mental health status and self-reported measures (PROMs): Clinician-led completion of the social and occupational functioning assessment scale (SOFAS) will be completed at each Outpatients visit. Self-reported PROMs using cross-cutting questionnaires will assess a range of outcomes such as Brain Injury Vision Symptom Survey (BIVSS for visual impairment), Patient Health Questionnaire (PHQ-9 for depression), General Anxiety Disorder (GAD-7 for anxiety), PTSD Checklist for DSM-5 (PCL-5 for PTSD), Suicidal Behaviour Questionnaire Revised (SBQ-R for suicide ideation), Alcohol Use Disorders Identification Test (AUDIT) and quality of life (EQ5D5L for alcohol abuse). All of these questionnaires are validated and widely used. These PROMs will be completed in paper format remotely and posted to the research team in stamped addressed envelopes which will be provided to each participant.

During the study, it may be that a diagnosis of psychiatric problems is found. If so, we will refer the patient to the care team for further support. We will also provide details of local voluntary organisations that can help. If a patient self-reports any suicidal thoughts or behaviours, they will be contacted by the care team to provide further support. In addition, we will provide details of dedicated organisations such as Samaritans, Campaign against living miserably (CALM), Papyrus, Childline or SOS Silence of Suicide. We will also direct them to contact someone they trust, their GP, call 111 or their mental health crisis team (if they have one) to talk over their issues.

7. Adverse Event Reporting

All investigations are routine clinical investigations or variants thereof that normally do not carry any appreciable risks of adverse events (AEs). The collection and reporting of AEs, however, will be in accordance with the UK Policy Framework for Health and Social Care Research and the requirements of the National Research Ethics Service (NRES) and Health Research Authority (HRA). Definitions of different types of AEs are listed in the table of abbreviations and definitions. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the study participant this should be documented in the source data with reference to the protocol. We will also follow University of Birmingham processes for safety reporting as per the Quality Management System: https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/qms.aspx.

8. Samples

Blood (7ml) and saliva (2-3ml) will be collected in standard tubes in the outpatients department of UHB and these volumes are routinely collected as part of standard care. Blood will be collected by the clinical care team by trained nurses/doctors. Saliva is collected by simply spitting into a special tube containing a stabiliser reagent. Needlestick injuries during blood collection are minimised by trained and competent nurses/doctors who will collect blood.

All samples will be transported by the research team and stored in labelled aliquots and in lockable, HTA compliant freezers. Samples will be transported to University of Birmingham labs and rendered acellular by centrifugation. Serum and saliva samples will then be aliquoted and stored in lockable freezers until required. Biomarkers will be detected in serum and saliva by enzyme linked immunosorbent assays (ELISA) using commercially available kits. See attached risk assessment form (COSHH human biological fluids).

After analysis, any remaining samples will be kept in locked University-owned freezers for up to 10 years or transferred to other ethically approved projects looking at serum and saliva biomarkers.

9. Data Handling and Record Keeping

9.1. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

All data should be recorded on and linked to electronic clinical record systems where possible. In addition, an electronic record of recruited patients, visits and tests performed and, where possible, results with dates will be kept in the site file.

9.2. Data Management

All missing and ambiguous data will be queried. Information will be handled as dictated by the Data Protection Act, 2018, and General Data Protection Regulations. All identifiable data including clinical records and images will form part of the patient's clinical record and so will be stored in NHS hospital servers in the usual way and will be subject to standard information governance procedures and care. If a participant or their consultees decide to withdraw, data will be retained and analysed as part of the study.

Prior to any research-related analysis (i.e. beyond clinical care) all scans and investigations and any data arising will be pseudo-anonymised with a specific numerical code (study number). The details of which patient matches which code will be stored on an NHS computer system, subject to standard information governance procedures and care. Hospital numbers may also be linked to the study number on encrypted university computers, protected with at least AES 256-bit encryption in addition to standard university password-

controlled account access. Anonymised data will be shared in a TBI data hub that is being developed by us with collaborators in Cambridge for future research, which will require a data request and scrutiny from a panel of reviewers including PPIE representatives with lived experience of TBI.

9.3. Archiving

Documents will be archived following the University of Birmingham Code of Practice for Research. It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source documents (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 10 years.

10. Quality control and quality assurance

10.1. Site Set-up and Initiation

All participating Principal Investigators will be asked to sign Trust documentation and supply a current CV and evidence of Good Clinical Practice (GCP) Training to the Trust Research and Development Department. All members of the site research team will also be required to sign a site signature and delegation log. Prior to commencing recruitment all sites will undergo a process of initiation and will have completed GCP training. Key members of the site research team will be required to attend either a meeting covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trust Research and Development Department must be informed immediately of any change in the site research team.

10.2. Monitoring

There is no specific monitoring requirement. Continuous data monitoring will ensure the credibility of the data. Source documents will be available for 'on-site monitoring' by the host Trust and external agencies.

10.3. Audit and Inspection

The Principal Investigator will permit study-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up.

10.4. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with the study or the protocol relating to the study. Sites should therefore notify the Research Governance Team at the University of Birmingham of any suspected serious breach of GCP and/or the protocol.

A copy is sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC.

11. End of Trial Definition

The end of study will be 2 years after initiation or 6 months after recruitment of the last patient, whichever is the earlier. The CI will notify the REC and sponsor of the end of the study.

A copy of the end of study notification as well as the summary report is also sent to the University of Birmingham Research Governance Team at the time of sending to the REC.

12. Statistical Considerations

12.1. Definition of Outcome Measures

The primary outcome measure will be the longitudinal changes in mental health status and quality of life. This will be defined using parameters outlined in the clinical assessments section. The secondary outcome will be longitudinal changes in fluid biomarkers of injury (e.g. glial fibrillary acidic protein (GFAP), S100β, tumor necrosis factor-α and myelin basic protein), visual function (e.g. visual acuity, contrast acuity, colour vision, visual field pupil reaction, focussing mechanism and eye movements, and brain injury outcomes assessed using the Glasgow outcome scale and Mayo-Portland Adaptability Inventory), other mental health status and PROMs.

12.2. Power Calculation and Statistical Analysis

Data obtained from all clinical examinations and laboratory tests will be compared between the first visit (Contact 1) and the subsequent follow-up visits (Contact 2-6). Many of these data are continuous and normally distributed as well as being repeated measures data of the same subjects. As such, repeated measures ANOVA will be used to determine changes over time. Data that are not normally distributed or numeric will be analysed using non-parametric tests. Linear mixed models, linear regression and analysis of covariance will be used for binary and ordinal outcomes as appropriate. Trial statisticians in the Birmingham Clinical Trials Team will be engaged for further statistical advice, if required.

This is a pilot study to evaluate longitudinal changes in fluid and visual biomarkers of brain injury, mental health status and self-reported quality of life measures in patients with TBI (civilian and military veterans). The sample size is based on:
1) statistical advice that in a pilot / feasibility study, 30 subjects in each group are recommended to allow estimation of the parameters of interest[32].
2) Based on Child's et al.[32] which showed a difference of 5um in global retinal nerve fibre layer thickness between boxers and controls, an average RNFL thickness of 101. Past experience in the concussion clinic suggests that we are able to follow 80% of patients at the 3-month point (i.e. only 20% lost to follow up). We based the power calculation looking for power to detect a 5um change in the repeated measures, assuming correlation of 0.9 between repeated measures of RNFL thickness (conservative given that in the absence of pathology, RNFL thickness varies very little). Simulated power calculations in R revealed that 24 participants with complete data (recruiting 30 and assuming a 20% drop out) would have >80% power to detect a 2µm change in RNFL thickness and 100% power to detect a 5µm decrease.

13. Ethical Considerations

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The study will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 2018 and the Human Tissue Act 2008.

Some research participants may receive a new diagnosis of cognitive impairment or PTSD at follow-up. This is of benefit in terms of access to appropriate support services but may have potential harms in terms of withdrawal and acceptance of the diagnosis. We will inform their care team so that they can receive the appropriate support and develop an action plan. If a patient self-reports any suicidal thoughts or behaviours, they will be contacted by the care team to provide further support. In addition, we will provide details of dedicated organisations such as Samaritans, Campaign against living miserably (CALM), Papyrus, Childline or SOS-Silence of Suicide. We will also direct them to contact someone they trust, their GP, call 111 or their mental health crisis team (if they have one) to talk over their issues.

Before any participants are enrolled into the study, the Principal Investigator is required to obtain local R&D approval. Sites will not be permitted to enrol participants until written confirmation of R&D approval is received by the Principal Investigator.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants. Both minor and substantial amendments will be submitted to the sponsor for review and approval prior to submission to the relevant regulatory authorities.

Professor Zubair Ahmed (CI) is a co-founder and a non-executive board member of a University of Birmingham-based spin-off company called Neuregenix Ltd. Neuregenix Ltd is a contract research organisation but will have no part in this study.

14. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 and General Data Protection Regulation 2018

Participants will be identified using only their unique study identification number on the Case Report Form and correspondence and all identifiable data retained on Trust computers. No identifiable data will be stored on University of Birmingham servers. Data may be linked to hospital number and name on Trust computers but pseudo-anonymised on University of Birmingham secure servers protected by AES 256-bit encryption. No patient identifiable data will be stored on individual computers. Data transfers between the University of Birmingham and UHB will conform to secure University of Birmingham and NHS policies.

All questionnaires will have a cover sheet that will include a unique participant ID number only. If a patient accidently includes their name, this will be redacted on receipt.

The Investigator must maintain documents (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected. These will be stored in locked cupboards in University of Birmingham premises and access controlled by the Investigator.

Representatives of the sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

After data collection is complete, study data will be anonymised.

15. Insurance and Indemnity

The University has in force a Public Liability Policy and/or Clinical Trials policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

16. Publication Policy

Results of this study will be submitted for publication in peer reviewed journals. The manuscript is the responsibility of the Chief Investigator and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the Chief Investigator and must be submitted in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the study was performed with the support of the University of Birmingham.

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Abbreviations and Definitions:

Term	Description
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial subject participating in the study which does not necessarily have a causal relationship with the treatment received.
Related Event	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event (SAE)	An untoward occurrence that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect • Or is otherwise considered medically significant by the Investigator** Comments: The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria. * Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. ** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious
Unexpected and Related Event	An event which meets the definition of both an Unexpected Event and a Related Event
Unexpected Event	The type of event that is not listed in the protocol as an expected occurrence.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial