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# Traumatic brain injury related changes in military veterans

**Submission date**
03/11/2023

**Recruitment status**
Recruiting

**Registration date**
18/12/2023

**Overall study status**
Ongoing

**Last Edited**
05/10/2026

**Condition category**
Injury, Occupational Diseases, Poisoning

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

## Plain English summary of protocol

Background and study aims
Traumatic brain injury (TBI) results from a violent blow or jolt to the head and occurs most commonly from motor vehicle collisions, falls and interpersonal violence. Military personnel are at high risk of TBI and in recent conflicts, UK military personnel sustained TBI caused by improvised explosive devices, rocket-propelled grenades and gunshot wounds. Most people affected had mild TBI (mTBI), which has emerged as a signature injury in military personnel (one that defines the consequences of the conflict on the soldiers involved). The symptoms of mTBI include memory problems, confusion and disorientation, problems articulating words, headache, dizziness and problems seeing. The problems often resolve soon after injury, but occasionally can last for a long time after the initial TBI. Worryingly, however, 1 in 5 people go on to develop mental health problems within 12 months after mTBI, with 75% experiencing mental health problems within 5 years. This suggests that the initial TBI results in permanent brain damage, causing mental health issues. The reasons why mental health problems develop in TBI patients are currently not understood. This study aims to understand the changes that occur after TBI in military veterans and correlate these with blood tests, changes in vision, clinical assessments of mental health and patient-reported outcomes for quality of life that encompass daily living and mood. This approach offers a comprehensive way of capturing data on multiple systems affected by TBI and allows us to monitor patient progression over time and pinpoint the changes that determine long-term outcomes in veterans.
This research will identify blood tests and eye signs that can diagnose and predict outcomes after TBI. This research will benefit the veteran population by helping to diagnose their symptoms early and to be able to put in place management options, including drug interventions, that will improve the lives of veterans. In addition, the research will benefit the wider veteran population by demonstrating that targeted research-led solutions can have a positive impact on day-to-day living and may support more engagement with researchers to find solutions to unique problems faced by veterans, once discharged from the military. This research will also be applicable to civilian TBI and hence provide additional benefits.
The aim of this study 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 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 quality of life in veterans with a TBI and inform rehabilitation strategies to increase optimal management opportunities.
The objectives of the study are: (1), 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; (2), 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; (3), to relate these changes after traumatic brain injury to understand how quality of life is affected by injury.

Who can participate?
Participants will be sought to include into three study groups: a control group with no previous history of TBI or head injury; an acute TBI group who are recruited within 14 days after a head injury, and a veteran group who have a diagnosis and head injury. Study participants must be over 18 years old, male or female, must have two eyes, the capacity to consent and a willingness to follow the study protocol and must not be pregnant if female. The control group should not have a prior history of TBI or head injury whilst the acute and veteran TBI groups must have a diagnosis of head injury to be eligible.

Control participants will have biofluids (saliva and blood) collected, complete ophthalmology assessments, psychiatric assessments, and patient-reported outcomes at enrolment and 6 months later. Acute TBI and veteran participants will complete the same assessments at enrolment and patient-reported outcome questionnaires 3, 6, 9, and 12 months later. Biofluids collection, psychiatric, and ophthalmology assessments will also occur 6 and 12 months after enrolment. Acute TBI participants will have an additional visit 1 month after enrolment consisting of all measures.

What does the study involve?
The researchers will collect blood on enrolment to the study and then again at 6 and 12 months whilst patient-reported outcomes, involving questionnaires, will be filled in by all patients on enrolment and every 3 months. Only for the blood collection is a visit to the hospital required whilst patient-reported outcomes can be filled in and posted in prepaid envelopes. The acute TBI and veterans groups will also receive in-hospital visual field assessments, clinician-led psychiatric assessment and blood collection on enrolment and at 6 and 12 months.

What are the possible benefits and risks of participating?
The risks of participating in this trial are minimal as they involve simple tests that are routinely performed by trained staff. Although there may be no direct benefit, it is hoped that an early detection of changes in eye structure and visual outcome after head injury may be of benefit to future patients with head injuries, by allowing early access to treatments.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
July 2022 to August 2028

Who is funding the study?
Office of Veterans Affairs at The Cabinet Office (UK)

Who is the main contact?
1. Prof. Zubair Ahmed, z.ahmed.1@bham.ac.uk
2. Lt Col Richard Blanch, richard.blanch@uhb.nhs.uk

# Contact information

### Type(s)
Public, Scientific, Principal investigator

### Contact name
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# Additional identifiers

### Integrated Research Application System (IRAS)
324684

### Central Portfolio Management System (CPMS)
57179

### Protocol serial number
RG_22_114

# Study information

### Scientific Title
Understanding how traumatic brain injury-related changes in fluid biomarkers affect quality of life outcomes in veterans

### Acronym
UNTANGLE

### Study objectives
Evaluation of candidate fluid biomarkers in blood and saliva from veterans who have suffered a traumatic brain injury (TBI), correlated 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 will allow us to predict long-term prognosis in veterans.

## Ethics approval required
Ethics approval required

## Ethics approval(s)
Approved 10/08/2023, North West - Haydock (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 1048181; approvals@hra.nhs.uk), ref: 23/NW/0203

## Primary study design
Observational

## Study design
Observational longitudinal case-control study

## Study type(s)
Diagnostic, Quality of life, Screening

## Health condition(s) or problem(s) studied
Traumatic brain injury

## Interventions
Participants will be sought to include into three study groups: a control group with no previous history of TBI or head injury; an acute TBI group who are recruited within 14 days after a head injury and a veteran group who have a diagnosis and head injury. Study participants must be over 18 years old, male or female, must have two eyes, the capacity to consent and a willingness to follow the study protocol and must not be pregnant (if female). The control group should not have a prior history of TBI or head injury whilst the acute and veteran TBI groups must have a diagnosis of head injury to be eligible. The researchers will collect blood on enrolment to the study and then again at 6 and 12 months whilst patient-reported outcomes, involving questionnaires, will be filled in by all patients on enrolment and every 3 months. Only for the blood collection is a visit to the hospital required whilst patient-reported outcomes can be filled in and posted to us in prepaid envelopes. As for the acute TBI and veterans groups, they will also receive in-hospital visual field assessments, clinician-led psychiatric assessment and blood collection on enrolment and at 6 and 12 months.

## Intervention Type
Other

## Primary outcome(s)
1. Fluid biomarker levels in blood and saliva including neuronal damage (neurofilament light chain (NFL), neuron-specific enolase-1 (NSE1); tau, ubiquitin C-terminal hydrolase L1 (UCL-H1) and S100 beta) and immune markers (interleukin-6 (IL-6), tumor necrosis factor-alpha (TNFα) C reactive protein (CRP), brain-derived neurotrophic factor (BDNF), calcitonin gene-related peptide (CGRP) and pituitary adenylate-cyclase-activating polypeptide (PACAP) as well as hormones such as cortisol will be measured by enzyme-linked immunosorbent assays (ELISAs) on enrolment and at 6 and 12 months.
2. Visual function tests including optical coherence tomography, visual field, visual acuity, colour vision, contrast acuity, and pupil reactivity will be tested on enrolment and at 6 and 12 months
3. Mental health and quality of life outcomes assessed using patient-reported questionnaires at

enrolment and at 3, 6, 9 and 12 months:
3.1. Social functioning measured using the social and occupational functioning assessment scale (SOFAS)
3.2. Visual impairment measured using the brain injury vision symptom survey (BIVSS)
3.3. Depression measured using the patient health questionnaire (PHQ9)
3.4. General anxiety disorder measured using the general anxiety disorder-7 (GAD-7)
3.5. Posttraumatic stress disorder measured using the PTSD checklist for DSM-5 (PCL-5)
3.6. Suicidal behaviour measured using the suicidal behaviour questionnaire revised (SBQ-R)
3.7. Alcohol use disorder measured using the alcohol use disorders identification test (AUDIT)
3.8. Quality of life measured using the EuroQoL Five-dimensional five-level questionnaire (EQ-5D-5L)

### Key secondary outcome(s)
There are no secondary outcome measures

### Completion date
01/08/2028

## Eligibility

### Key inclusion criteria
Acute TBI group:
1. Over the age of 18 years
2. Must have two eyes
3. Capacity to consent
4. Willing and able to follow the protocol
5. Moderate or severe head injury requiring admission to the Queen Elizabeth Hospital within the prior 14 days

Veterans with TBI group:
1. Over the age of 18 years
2. Must have two 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

Healthy control group:
1. Over the age of 18 years
2. Must have two eyes
3. Capacity to consent
4. Willing and able to follow the protocol
5. No prior history of moderate or severe TBI

### Participant type(s)
Healthy volunteer, Patient

### Healthy volunteers allowed
Yes

### Age group

Mixed

### Lower age limit
18 Years

### Upper age limit
100 Years

### Sex
All

### Total final enrolment
0

### Key exclusion criteria
Exclusion criteria for all 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, any known retinal or optic nerve disorder of either eye, pregnancy

Additional exclusion criteria for the control group only:
Patients have not suffered a TBI or head injury

### Date of first enrolment
01/11/2023

### Date of final enrolment
30/07/2027

## Locations

### Countries of recruitment
United Kingdom

England

### Study participating centre
**University Hospitals Birmingham**
Mindelsohn Way
Edgbaston
Birmingham
England
B15 2TH

## Sponsor information

**Organisation**
University of Birmingham

**ROR**
https://ror.org/03angcq70

# Funder(s)

**Funder type**
Government

**Funder Name**
Office of Veterans Affairs, The Cabinet Office

# Results and Publications

### Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Professor Zubair Ahmed (z.ahmed.1@bham.ac.uk). The type of data that will be collected in this study includes standard medical history, human biofluids as well as visual imaging and data from questionnaires. Pseudo-anonymised project data will be transferred from UHB's electronic systems and stored and hosted by the University of Birmingham (UoB) with access to authorised individuals protected by individual usernames and passwords. Captured data will be in the scale of a few hundred gigabytes, which are easily stored on UoB's secure servers. UoB is ISO27001 compliant for data security and confidentiality. Participants will be allocated a numerical identifier and these anonymous identifiers will be used throughout the study so that names do not appear on individual records. All participant paper files will be kept confidentially in a secure location and transferred to Prof Ahmed and UoB for long-term safe storage.

### IPD sharing plan summary
Available on request

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Protocol article | | 19/08/2024 | 20/08/2024 | Yes | No |
| Participant information sheet | Acute TBI study group version 2.1 | | 06/11/2023 | No | Yes |
| Participant information sheet | Control study group version 2.1 | | 06/11/2023 | No | Yes |
| Participant information sheet | Veterans study group version 2.1 | | 06/11/2023 | No | Yes |

| | | | | |
|---|---|---|---|---|
| Protocol file | version 3 | 06/11/2023 | No | No |