

PARTICIPANT INFORMATION SHEET (mTBI variability)

mTBI-Predict

Mild Traumatic Brain Injury Biomarker Study, a prospective cohort biomarker study of military and civilian participants with mTBI

What is this research for?

- Mild traumatic brain injury (or mTBI), commonly called concussion
- We don't always know how a brain injury will affect people's health
- This study will test members of the public, service personnel and sports people to find ways to help us predict how a brain injury will affect people's health
- This will help us treat people better, getting them back to work, duty or play quicker

Do I have to take part?

- No! Joining the study is voluntary. If you decide not to take part, your usual care will not be affected
- Please take the time to read this information sheet fully and talk to others about the study if you wish
- You will be able to discuss the study with a member of the research team and ask any questions you might have

Will I be paid for taking part?

We will help with travel and parking costs and offer compensation for your time

Where can I get more information?

- Part 1 tells you what will happen to you if you choose to take part
- Part 2 gives more detailed information about the conduct of the study

For questions about the study please contact:

<Insert local contact name and telephone number>

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Part 1 – about the mTBI-Predict study

What is this research for?

There are nearly a million hospital visits each year in the UK for mild traumatic brain injury, or mTBI. This is sometimes called concussion. We call it “mild” but a third of people can’t work a year after their injury. Problems can include headaches, poor memory, and poor mental health.

We can’t always tell which patients might have long-term problems so we can’t always give people the right early treatment.

Biomarkers are things like blood samples or brain scans. We are going to test many different biomarkers to see which can show who is at risk of long-term health problems after mTBI. We want to find biomarkers that are accurate and practical for civilians, soldiers and sports people.

Why have I been invited?

We are asking you because you have had an mTBI in the last 3 weeks and are over 18.

Do I have to take part?

No, this is entirely up to you. Taking part is voluntary. You don’t have to take part if you don’t want to. This will not affect your standard of care. We are giving this information for you to consider carefully before you decide. You can discuss it with family or friends. If there is anything unclear, please speak to a member of your care team or the research team.

What would taking part involve?

If you decide to take part, we will ask you to do the following over the next 2 years:

Three weeks after your injury (visits 1, 2 and 3)

- Complete an Informed Consent Form
- Have 3 research visits:
 - a remote test visit, using an app, including a 6-minute walk
 - a clinical assessment day at a hospital, with a phone call the day before
 - a brain scan day at an imaging centre

Three weeks after your injury (visits 4, 5 and 6)

- EITHER
 - Repeat the clinical assessment day three more times in 12 days
- OR
 - Complete the brain scan day three more times in 12 days
- Complete some memory and brain health tests for 5 minutes a day for 2 weeks after your visits, using the study app
- Complete a headache and sleep diary daily for until visit 8 (nearly 3 months)
- Give weekly saliva samples until visit 8

Two months after your injury (visit 7)

- Complete some memory and brain health tests for 5 minutes a day for 2 weeks, using the study app
- Remote tests using the study app

Three months after your injury (visits 8, 9 and 10)

- Have 3 research visits:
 - a remote test visit, using the study app, including a 6-minute walk
 - a clinical assessment day at a hospital, with a phone call the day before
 - a brain scan day at a university
- Complete some memory and brain health tests for 5 minutes a day for 2 weeks after your visit, using the study app

Six months after your injury (visit 11)

- For the month before your visit, wear the smartwatch and complete a headache and sleep diary daily. Do a weekly memory and brain health test (5 minutes)
- Once: Remote tests using the study app, including a 6-minute walk

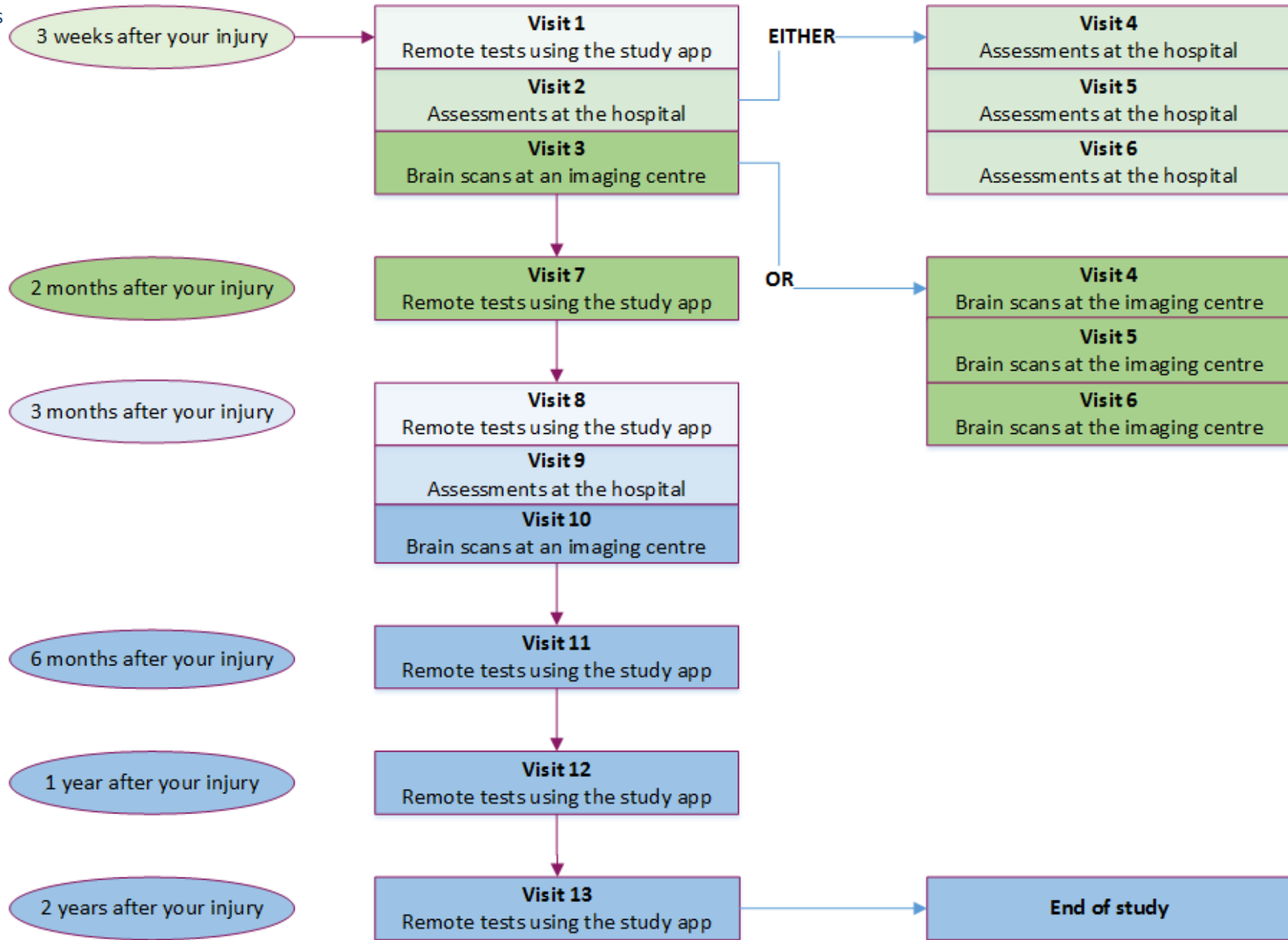
One year after your injury (visit 12)

- For the month before your visit, wear the smartwatch and complete a headache and sleep diary daily. Do a weekly memory and brain health test (5 minutes)
- Once: Remote tests using the study app, including a 6-minute walk

Two years after your injury (visit 13)

- For the month before your visit, wear the smartwatch and complete a headache and sleep diary daily. Do a weekly memory and brain health test (5 minutes)
- Once: Remote tests using the study app, including a 6-minute walk

Figure 1 – Study visits



What will I be asked to do if I agree to take part?

If you take part, there will be 13 study visits over the next 2 years. This includes 10 study visits with 3 of either the clinical assessment days or the brain scan days repeated. Some of these will be a day at a hospital or university, and some will be much shorter, done at your home on your phone or tablet.

When you first join the study

If you consent to join the study, we'll book your first visits and help you to install the study app on your personal device. This is free and doesn't take up much space or data. We'll also give you a Garmin smartwatch to use with the app to collect data about yourself during the study. The smartwatch can be taken off when you are not performing study visits. **You will be able to keep this smartwatch after completing the study.**

Remote tests using the study app (visits 1, 7, 8, 11, 12 and 13)

The first "visit" will be at home using the study app. You will get a notification to do your tests.

There will be a set of tests looking at how your brain functions doing different tasks. Everyone will do a practice run before any proper tests, to get used to them. These tests are on a database called Cognitron which is already used in brain research across the country. These memory and brain health tests should take about 30 minutes to complete.

The app also has questionnaires about your headache, vision, balance, mental health and sleep. These questionnaires should take about 30 minutes to complete.

Remote test visits will be done at 3 weeks, 2 months, 3 months, 6 months, 1 year and 2 years after your injury. Except at 2 months, this remote test will involve a 6-minute walk test. This is a walk in the street or park, wearing the Garmin smartwatch. You should try to do it in the same place each time. **After the 2 year tests you finish the study.**

There is also a symptom diary. This is to record any headache and sleep symptoms daily for 3 months – this should take a couple of minutes to do each day. You'll also do a 5 minute memory tests 5 times a week for 2 weeks.

What do we want to collect between visit 3 and visit 8?

- Complete some memory and brain health tests for 5 minutes daily for 2 weeks
- Smartwatch data – daily movement data over 3 months
- Daily headache and sleep diary using the study app

What do we want to collect just before visit 11, 12 and 13?

- For the month before your visit, wear the smartwatch and complete a headache and sleep diary daily. Do a weekly memory and brain health test (5 minutes)
- Remote tests using the study app, including a 6-minute walk test.

Assessments at the hospital (visits 2 and 9)

Before the hospital assessment day, the study doctor will call you to ask you questions about yourself including personal details, your injury and past medical problems. We also want to know detailed questions about any headaches, balance or hearing problems, and mental health. This phone call could take at least an hour.

These assessment days take place at <<insert local site details>>.

The visit will start early. You will be provided with a light breakfast and lunch. We will also reimburse you if you wish you buy your own lunch.

First, a researcher will take some blood samples (around 2 teaspoons, or 8mls). Then you will give a saliva sample by spitting into a sample pot. You'll be asked to give a urine sample. Finally, they will measure your height, weight, and blood pressure.

The doctor and a physiologist will then do various tests looking at balance, hearing, vision and cerebral physiology (how the brain works). These tests are split into sections below.

Vision tests (about 60 minutes):

1. Seeing letters from far away using the same letter chart as at an optician.
2. How well your eyes can detect contrast and colour and react to light, which will include shining a bright light at your eye.
3. How well your eyes see objects at different distances.
4. Measuring your field of vision, using a Humphrey's Visual Field Analyzer.



A Humphrey's Visual Field Analyzer



An Optical Coherence Tomography scanner

5. Looking at the nerves and blood vessels in the back of the eye. We do this with a scanning laser often used in clinical practice, called Optical Coherence Tomography, or OCT.

Balance and hearing tests (about 90 minutes):

Balance tests

1. There will be tests where you are sitting, lying or standing, in the dark or in the light. You will look at a computer screen for some of the tests and you will respond by pressing a button or by answering verbally.
2. In some of the tests you'll be moved on a motorised chair or you will need to stand still on a platform with either a soft or hard surface. This chair is specially designed and built to test how well people can feel movement and direction.
3. We'll record your responses to tests like static and moving images and lights.

Walking balance tests

1. Walking balance tests where you walk across the room. A researcher will walk alongside you to make sure you don't fall.
2. For some balance and walking tests we will use eye tracking software to see how your eyes move to keep your balance.
3. We'll also measure your brain signals using an EEG cap (electroencephalography, which measures electrical activity) set up on your head.

Cerebral physiology tests include different equipment and tasks (about 180 minutes, with a break):

1. A dual NIRS (near-infrared spectroscopy) and EEG cap will be set up on your head. The NIRS measures oxygen in the blood within the brain. First you will sit down calmly and quietly to measure your resting state. Then you will do a computer task.
2. Next you will be asked to contract your finger muscle whilst having a Transcranial Magnetic Stimulation applied. This uses a magnet to activate nerves in your brain. This will make the muscle in your finger twitch but is not painful.



The dual NIRS-EEG headset



The NIRS headset used in step 3

3. A different NIRS headset will then be fitted with two ultrasound probes (called “transcranial doppler”) on your temples which measure blood flow in your brain. You will be asked to lie back to measure your rest again. You will then do the computer task again from step 1.
4. Staying lying down, you will be fitted with a mouthpiece to breathe room air for 4 minutes, followed by 4 minutes breathing from a bag with a carbon dioxide enriched air mixture. You will be asked to breathe normally, but you might breathe slightly faster when breathing from the bag. You can take the mouthpiece away at any time, if you need to. After breathing from this bag, you’ll then be asked to breathe room air again, but at a faster rate for 2 minutes.
5. You will be asked to do 2 sets of stand to squat movements for 5 minutes, with a 10 minute rest between each set.
6. Last of all, we will ask you do 6 minutes of hand grip exercise while seated on a machine to measure the oxygen and blood flow in your brain.

The whole hospital visit

The whole visit starts at 8 or 10 am and finishes around 4 or 6 pm. We know it’s a long day and there will be complimentary morning hot drinks and biscuits, with a break for lunch which will be provided and an afternoon hot drink and biscuit break.

You will either repeat this hospital visit 3 extra times, or repeat the brain scan day described in the next section 3 extra times.

Figure 2 – Clinical day at the hospital

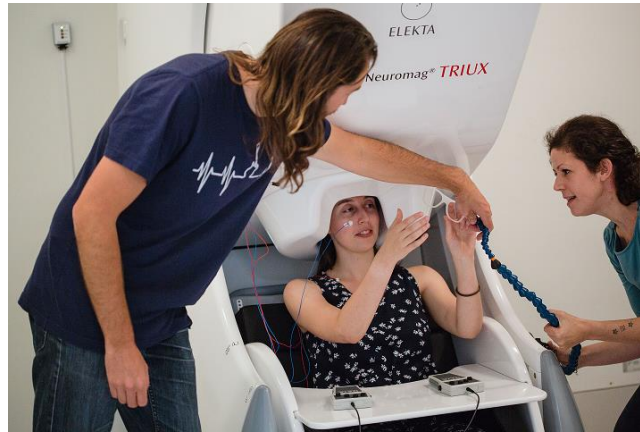


Brain scan days (visits 3 and 10)

What happens on the imaging assessment day?

This will take place in Stanford Hall, Birmingham, Aston or Nottingham. On your visit day, you will have one MEG session and then two MRI scan sessions in the MRI suite (detailed below).

Right: MEG scanner



Before your scan sessions

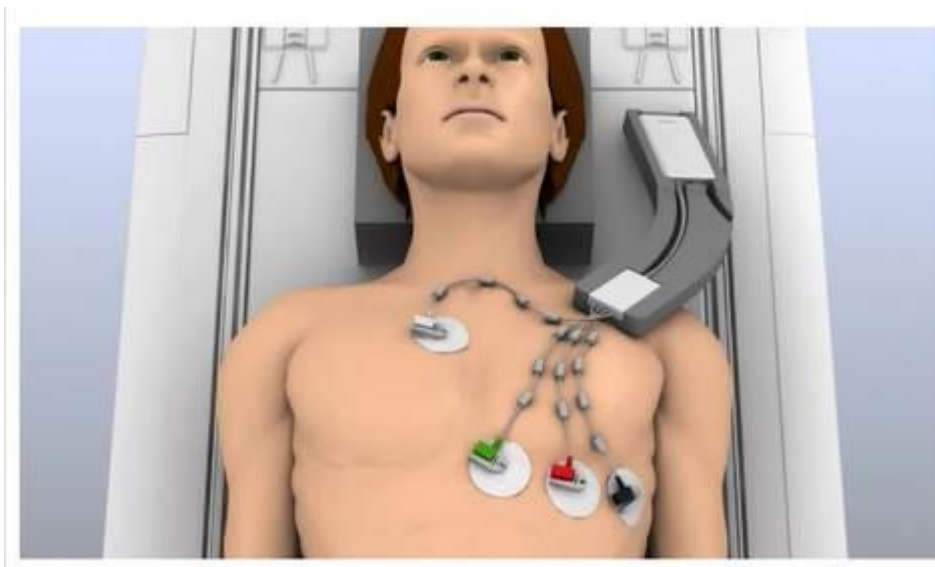
Before each session you will have some time (15-30 minutes) to get changed into scrubs. What you will need to do in the scanner will be explained. You will be asked to complete a safety questionnaire before your scan to make sure you are safe to be scanned. This is done every time MEG or MRI scans are done and it is important you answer all the questions as accurately as possible. It will ask about things like whether you have any metal in your body.

Below: MRI imaging suites at 3 possible sites: University of Birmingham (left); University of Nottingham (middle), Aston University (right)



What is a MEG scan and what will happen?

A MEG scan measures the tiny magnetic fields generated by your brain. There will be one MEG session per visit. At the beginning of this session we will take 30 minutes to prepare the MEG. You will be able to get familiarized with the equipment and procedures for the tests. The researcher will also use this period to put some electrodes on your body that will help us track the heart rate and position of your head and eyes in the MEG system. . If you have a hairy chest you may be asked to shave, or cut closely with scissors, an area on your chest in order for the electrodes to adequately stick to your skin. The image below demonstrates how the electrodes will be attached to your chest.



After the preparation you will do some tasks while the researcher records your brain activity in the MEG. You will be presented with things like a visual display or tones. You will be told how to respond to these, for example by pressing a button. Throughout the tasks you will need to keep your eyes focused, but there will be some sections where you will be able to freely move your eyes and relax. In total, the MEG session will last about 90-120 minutes.

What is an MRI scan and what will happen?

An MRI scan creates images of the brain or other parts of your body.

You lie on a table inside a cylindrical machine which uses magnetic fields and radio waves (not x-rays) to take pictures of your brain. To get good pictures, it is very important to stay still during the scan. Positioning aids will keep your head from moving and you should try to relax.

The scan itself is a harmless, non-invasive procedure but it is noisy. Some people can feel uncomfortable whilst lying in the scanner tube. There will be two MRI scan sessions on the visit day and will each take about an hour.

For each MRI session, you will have some time (30-60 minutes) before going into the scanner to get changed and the details of what you will need to do in the scanner will be explained.

Any equipment which is needed for the scan sessions will be set up on you. The researcher will record your heart rate and breathing with a belt around your chest, and a set of sticky pads on your chest will also monitor your heart rate. The 2 sessions will be separated by at least 30 minutes so you have a good break and can walk around. You will be able to talk to the researcher during the scans by using the scanner's intercom.

What are the MRI tasks?

In the first MRI session we will take measurements of your brain structure while resting. You will then be asked to carry out a cognitive task whilst in the scanner. This allows us to take measurements of your brain structure whilst active.

The second MRI session will again mostly be you lying still and relaxed. We will take some measurements of the blood flow in your brain. Then we will give you a mouthpiece to breathe through. We will give you a carbon dioxide enriched air mixture through this mouthpiece and you'll be asked to breathe normal room air then the carbon dioxide air mixture and back to room air. You will be asked to breathe normally throughout, but you might breathe slightly faster when breathing the carbon dioxide mixture. You will be able to remove the mouthpiece during the test if you need to.

Figure 3 – Brain scan day



Are the tests safe?

All of the tests we will ask you to do are already done in the NHS. The possible risks are:

- Bruising from the needles used to take blood samples
- Dizziness or nausea from some of the balance tests (we can offer you a travel sickness pill if this happens)
- Feelings of claustrophobia in the MRI scanner

What are the possible disadvantages and risks of taking part?

Apart from the possible risks described above, we know we are asking for a lot of your time, with a lot of tests.

There is a small chance that we may discover something in your brain scans that you were not already aware of, that may require further investigation. If this is the case a member of our clinical team will discuss this with you and direct you to appropriate support.

There is the possibility of incidental findings being made that would come with career implications. These implications would depend on the nature of the finding, the most likely occurring as a result of brain imaging. However, all military participants with head injury would have brain imaging completed as standard of care, routine imaging would have the same pick-up rate for relevant incidental findings as the study imaging paradigm, as such there is no additional burden. The blood testing is limited to potential biomarkers of brain trauma and hormone testing, as such it is unlikely that there would be incidental findings with clinical and career consequence.

What are the possible benefits of taking part?

There will be no immediate benefit to you for taking part, but our aim is to improve treatment for people with mild traumatic brain injury and concussion in the future.

Will I get paid for taking part?

You will be eligible for Experimental test allowance; the research team will action this via RCDM admin office with payment made via JPA. Clinical days will be eligible for 27 instances of the allowance and imaging days for 13. We can also pay for your travel expenses. Please ask one of the researchers for more details.

What will happen to the results of the research study?

We will publish our results in medical journals and present them at scientific conferences, to help doctors to learn, and for patients to benefit. When you enter the study you will be asked if you wish to be informed of the trial results, and whether you wish to be informed by email or post. The results will also be made available on the mTBI-Predict trial website (www.birmingham.ac.uk/mtbi-predict).

PART 2 – further details on how this study is run

How have patients and the public been involved in this study?

Patients and the public, including civilians, military, and sports people, have been involved in developing this study. We have asked about what is important to test, what seems acceptable from the point of view of how much we are asking people to do, and how the study information is put across.

This study is entirely in the hands of very experienced researchers and no patient group or lay person can influence your treatment or get access to your personal healthcare records.

What if I do not want to carry on?

You can stop being a part of the study at any time, without giving a reason, but we will keep information about you that we already have. You will also be withdrawn from the study if anything happens to you which means you are no longer able to provide informed consent. If you do stop being part of the study, for any reason, we will keep information about you that we already have.

If you stop taking part in the study, we would still like to collect information about your health from the NHS. If you do not want us to do this, please let us know.

What if something goes wrong?

We do not foresee any problems due to taking part in the study. However, all participants are covered for negligent harm according to NHS indemnity guidelines. If you have a concern about any part of this study, you should ask to speak to one of our researchers who will do their best to answer your questions.

The University of Birmingham also arranges clinical trial insurance which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the study. The insurance may alternatively, and at the University's discretion, provide cover for non-negligent harm to participants.

As this research study will involve both military personnel and civilians, the Ministry of Defence (MoD) maintains the 'No Fault Compensation Scheme' specifically for the payment of no-fault compensation to, or in respect of, a volunteer who suffers illness and/or personal injury as a direct result of participating in research conducted on behalf of the MoD. The no-fault compensation arrangements apply to research participants (Military, Civilian, or non-MoD) who take part in a trial that has been issued with favourable opinion by the MoD Research Ethics Committee.

A research participant wishing to seek no-fault compensation under these arrangements should contact the Directorate of Judicial Engagement Policy, Common Law Claims and Policy (DJEP-CLCP), Ministry of Defence, Level 1, Spine 3, Zone J, Whitehall, London, SW1A 2HB who may need to ask the Claimant to be seen by a MoD medical advisor.

If you wish to complain about any aspect of the way you have been approached or treated during this study, the normal NHS complaints mechanisms will be available to you. Copies of these guidelines are available on request. If you wish to complain about how you have been treated during this study please contact the Patient Advice and Liaison Service (PALS) or the Complaints Team at your local hospital. The contact details are at the end of this Information Sheet.

How will my personal data be kept secure?

Your information passed to the University of Birmingham will be safely and securely stored and kept strictly confidential under the Data Protection Act 2018 in the same way as all of your other medical records. Any electronic data will be stored securely on our password protected University of Birmingham servers. We will not share any data that can identify you with any other third party.

What data will we be collecting and what will we use it for?

We will ask for your consent before collecting your personal data listed in the table below.

When	What data will be collected
Joining the study	<ul style="list-style-type: none"> • Full name • Email address and/or mobile number • Date of birth, sex at birth, NHS number • Online questionnaires • Smartwatch movement data
Remote visits 1, 7, 8, 11, 12 and 13	<ul style="list-style-type: none"> • Online questionnaires including cognition, mood, headache, sleep, also some smartwatch movement data
Hospital visits 2 and 9	<ul style="list-style-type: none"> • The same details as visit 1 if not already collected

	<ul style="list-style-type: none"> • Relevant medical history • Physical assessment data collected during this visit
Brain scan visits 3 and 10	<ul style="list-style-type: none"> • Brain images and assessment task data

Your hospital will collect information from you, your medical records and your GP for this research. Your hospital will use your name, NHS number and contact details to contact you, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Your hospital will pass these details to the University of Birmingham along with the information collected from you and your medical records and will be used exclusively for this research.

Individuals from the University of Birmingham may look at your medical and research records to check the accuracy of the research and that it is being done properly. At the University of Birmingham only people who need it will have access to information that identifies you. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

If you consent to it, the researchers involved in the study may, in future, access data from your central NHS records, for example through NHS Digital. This will give researchers information that is already collected during your GP and hospital visits, and lets researchers find out about your health after the study has ended without needing to contact you again. To do this, we would send your name, gender, date of birth and NHS number with any request for information. If you don't want us to do this, just let the research team know.

What data will be shared?

Research data will be shared between collaborators and researchers working on the study at the institutions who are involved in it.

People who do not need to know who you are will not be able to see your name or contact details. Instead your data will be pseudonymised. This means that an ID code will replace your name. Your brain scans, for example, will be sent to a secure University of Birmingham data server and made available for the investigators and researchers who are working on the project to analyse but none of these people will be able to see who you are.

Data will also be shared with other researchers, whether private, academic or commercial, in the UK or abroad including the US. Data may be made available to other researchers via an open access database. This is good practice so scientific research can be shared and checked. In this case all shared data will be fully anonymised and will never contain any personal details about you (name, address etc.). It will be impossible for anyone to identify you.

What will happen to the samples I give?

The blood and urine samples will be stored first in the laboratory at the hospital in which you have been seen, where they will be processed and some sent to the central study laboratory at the University of Birmingham for storage and analysis.

Your saliva samples will be posted directly to the central study laboratory at the University of Birmingham for storage and analysis.

Your samples will only be identified by your study ID code. They will be kept for 2 years after the end of the study to allow time for the samples to be analysed. After this, excess samples will be stored in the University of Birmingham Human Biomaterials Resource Centre biobank or be destroyed.

How long will my personal data be kept?

Your data will be kept for at least 25 years once the study has finished. Your contact details will be deleted after the study finishes and any central NHS data is collected.

Who is the data controller?

The University of Birmingham, Edgbaston, Birmingham B15 2TT is the data controller for the personal data that we process in relation to you. This means that the University is responsible for looking after your information and using it properly.

What is our legal basis for processing your data?

The legal justification we have under data protection law for processing your personal data is that it is necessary for our research, a task we carry out in the public interest. This means that it is a legal requirement that the data we collect about you is only used for research purposes to benefit public health. The data will not be used to make decisions about you.

What are your choices about how your information is used?

We need to manage your data in specific ways for the research to be reliable and accurate. This means that we won't be able to let you see or change the data we hold.

The University of Birmingham takes great care to ensure that personal data is handled, stored and disposed of confidentially and securely. Staff receive regular data protection training and the University has put in place organisational and technical measures so that personal data is processed in accordance with the data protection principles set out in data protection law. More information on how the University processes personal data can be found on the University's website on the page 'Data Protection – How the University Uses Your Data' (<http://www.birmingham.ac.uk/privacy/index.aspx>).

Where can I find out more about how my information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- in the leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by contacting the Data Protection Office, Legal Services, The University of Birmingham, Edgbaston, Birmingham B15 2TT
Email: dataprotection@contacts.bham.ac.uk Telephone: 0121 414 3916

Who is organising and funding the study?

The study is sponsored by the University of Birmingham, which means the University of Birmingham has certain legal and ethical responsibilities for the study (reference RG_22-004). It is being coordinated by the Birmingham Clinical Trials Unit (BCTU) and it is funded by the

government <<xxxx (ref: xxxx)>>. The chief investigator for the study is Professor Alex Sinclair, Professor of Neurology, based at the University of Birmingham.

Will my GP be informed of my involvement?

If you agree to it, we will tell your GP that you are taking part and if they need to know of any test results.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people who protect patient interests. This group is called a Research Ethics Committee. This study was reviewed and granted favourable opinion by the Ministry of Defence Research Ethics Committee before it started.

Who can I contact for further information?

Thank you for taking the time to read this information and for considering taking part in our study. If you need more information or would like to speak to someone please contact:

Name	<<insert local details>>
Job title	<<insert local details>>
Contact Details	<<insert local details>>

If you would like independent advice about taking part in research you can contact the NHS Patient Advisory and Liaison Service (PALS) for support:

Local PALS contact/Hospital Advisory Service number(s)	<<insert local details>>
Local PALS/Hospital Advisory Service e-mail address	<<insert local details>>

You can also contact the mTBI-Predict study team:

mTBI-Predict study office
Birmingham Clinical Trials Unit
Public Health Building
University of Birmingham, B15 2TT
Email: mtbi-predict@trials.bham.ac.uk

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The views expressed are those of the author(s) and not necessarily those of the.>>