Biomarkers for RAtional Investigation for Neurological Decision Support in traumatic brain injury cohort study with a nested pragmatic randomised trial

Clinician Information Sheet

BRAINS-TBI

Head injury is a common Emergency Department (ED) presentation, but only a small proportion of patients (approximately 7%) undergoing CT have clinically significant traumatic brain injury (TBI).

Following a brain injury, specific proteins (biomarkers) are released into the blood including **GFAP** (glial injury marker) and **UCH-L1** (neuronal injury marker). Biomarkers are not currently recommended for use in the NICE Head Injury Guidelines [NG232] and need more evidence of clinical utility, safety and cost-effectiveness.

We are recruiting patients to a cohort study with a sub-set also being recruited to a nested RCT to answer two key questions:

1) Can we use biomarkers to reduce the number of CTs (**BRAINS-TBI CT**)? This nested RCT will only include patients where there is equipoise about ordering a CT head. We are calling these "medium risk", defined according to NICE NG232 criteria. Please see next page for the criteria.
2) Can blood biomarkers help to identify patients at higher risk of having ongoing symptoms for months after their injury (**BRAINS-TBI Cohort**). This prognostic cohort study will include all recruited patients, including those in the RCT.

Who will be recruited?

- Patients who present within 24 hours of sustaining a head injury that needs assessment for a CT head using NICE Head Injury Guidelines (NG232) and have a GCS of 13-15. We are being as pragmatic as possible with recruitment to ensure the patients reflect those who we see in our clinical practice in routine NHS emergency care.
- For **BRAINS-TBI Cohort** patients can be ≥16 years. For **BRAINS-TBI CT** patients need to be ≥18 years due to the regulatory requirements using the PoC device.

What will happen in the ED when a patient is recruited?

- **BRAINS-TBI Cohort** – patients will have blood taken as soon as possible after recruitment and again 2 hours later. These samples will be stored for a large number of candidate biomarkers to be tested. The two time points will enable us to understand early biomarker trajectories and whether change over time is more informative than a single value.
- **BRAINS-TBI CT** – Only NICE medium risk patients are eligible and will have blood tests as per the BRAINS-TBI Cohort study. They will also be randomised to usual care or biomarker led care.
  For the **Usual Care arm** the patient should have a CT as per usual clinical practice.
  For the **Biomarker Led Care arm** at time of blood sampling the Abbott i-STAT Alinity point-of-care device will also be used. This device takes ~13 minutes to provide GFAP and UCH-L1 levels.
  - The research team will provide the results, and the thresholds will be clearly indicated. If at either time point one of these biomarkers are raised above threshold the patient should have a CT head. If they are both below threshold at each time point, and there has been no neurological worsening during observation, then no CT head is indicated according to the biomarker-guided pathway - however final decision rests with the treating clinician.
  - The device being used has UKCA and FDA approval for this indication and current evidence supports these thresholds as safe. By doing the sampling at 2 time points we are building in both an observation period and double testing as an additional safety layer beyond current regulatory requirements.
  - We would encourage clinicians to follow this decision-making pathway for patients allocated to the biomarker-led arm. Avoiding crossover between trial arms is important to ensure the study can reliably determine whether PoC biomarkers are useful and safe in guiding CT decision-making. However, we recognise that **clinical judgement should always take precedence.**

Why do we need to recruit patients before they have their CT head?

- Most previous studies have collected biomarker samples after CT imaging, limiting our ability to determine whether biomarkers could safely reduce CT use in routine practice.
- Recruiting patients before CT reflects how biomarkers would be used in real ED workflows and allows a robust evaluation of safety, feasibility and potential impact in an NHS setting.

We recognise that participation may delay discharge for a very small number of patients. We are grateful to the clinical teams facilitating recruitment and to the patients taking part, and hope that the evidence generated will reduce future length of stay.

Could I be asked to assess if a patient can participate as an Independent Clinician?

Yes. In England and Wales if a patient lacks capacity to consent to research, the Mental Capacity Act 2005 requires a personal consultee, or if none is available, a nominated consultee (which may be a clinician independent of the research team) to advise whether a patient would want to take part. If the patient later regains capacity, or if a family member willing to act as personal consultee becomes available, informed consent will be sought at that time.

What else are we asking patients to do?

- Where possible patients will fill in some short questionnaires in the Emergency Department. We will then follow them up by phone/mail/online at ~2 weeks, 3 months and 6 months with a set of questionnaires and neurocognitive tests. The core outcome measures take about 15 minutes to complete.
- Patients will be sent a £20 voucher at the end of study as a token of appreciation for their time to take part.

This study is funded by the NIHR EME programme (NIHR159241).

Trial websites: https://norwichctu.uea.ac.uk/brains-tbi/ and https://www.tbiresearch.co.uk/brains-tbi-information-for-clinicians

If there are any questions or you wish to find out more please contact: Study team (pocket.study@uea.ac.uk), Chief Investigator Virginia Newcombe (vfjn2@cam.ac.uk) or Co-Lead Fiona Lecky (f.e.lecky@sheffield.ac.uk)

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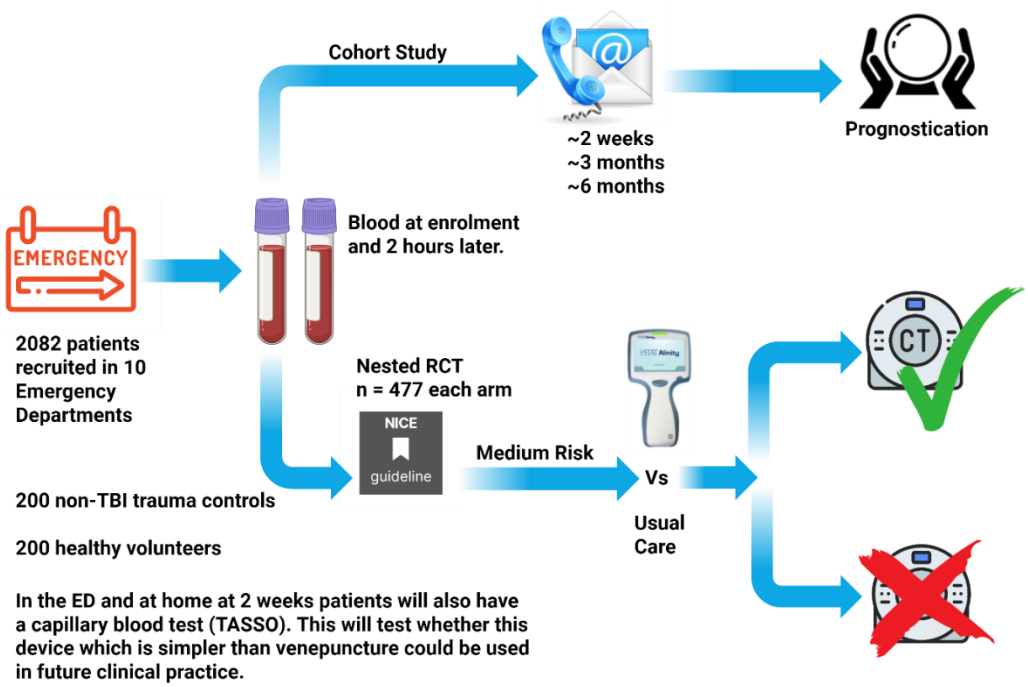
BRAINS-TBI Cohort Inclusion Criteria:	Exclusion criteria:
• **≥ 16 years of age** and • Glasgow Coma Score 13, 14, or 15 and • Presentation within 24 hours of head injury and • Meet criteria to be assessed for a head CT using NICE Guidelines (NG232). • Patients with a prior history of TBI more than 1 year prior may still be included.	• Participant without capacity and no personal or professional consultee (legal representative). • Participant with capacity unwilling to provide informed consent • Unable to adequately understand written and verbal English for consent and assessments unless an appropriate translator is available.

BRAINS-TBI CT: This nested RCT focuses on **medium-risk patients (defined as below in NICE Head Injury Guidelines)**, where there is most potential to safely reduce CT scanning. All patients in this nested RCT will be also in the BRAINS-TBI Cohort. Please check inclusion criteria with research team prior to recruitment (amendment pending).

Inclusion Criteria **(Medium Risk Group):**	Exclusion criteria:

• **Age ≥ 18 years of age** and
• Glasgow Coma Score back to 15 or baseline within 2 hours of injury and
• Presentation within 24 hours of head injury and
• When assessed using NICE NG232 clinical decision support tool found to be back to GCS 15 or corroborated baseline GCS of 13 or 14 within 2 hours post injury **AND have**:
• **EITHER** Loss of consciousness or amnesia **PLUS** any of:
  ◦ Age 65 years or over
  ◦ Any bleeding or clotting disorders (liver failure, haemophilia, taking anticoagulants or antiplatelets (not including aspirin)
  ◦ Dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle, or fall from a height of more than 1m or 5 stairs)
  ◦ More than 30 minutes' retrograde amnesia of events immediately before the head injury
• **OR** no loc or amnesia but head injury and taking anticoagulant or antiplatelet agents, excluding aspirin monotherapy, where shared decision making is positive for CT.
	• Low risk TBI and so CT scan NOT recommended according to NICE-CDR
	• Significant extra-cranial injury for which a full trauma CT or CT neck with head would usually be indicated.
	• Any NICE Guideline (NG232) high risk criteria for which a CT scan IS recommended within 1 hour
	  ◦ GCS ≤ 12 on initial assessment in the ED
	  ◦ Not back to GCS 15 or an independently corroborated pre-injury baseline GCS of 13-14 within 2 hours of injury
	  ◦ Suspected open or depressed skull fracture
	  ◦ Any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign)
	  ◦ Post-traumatic seizure
	  ◦ Focal neurological deficit
	  ◦ More than 1 episode of vomiting



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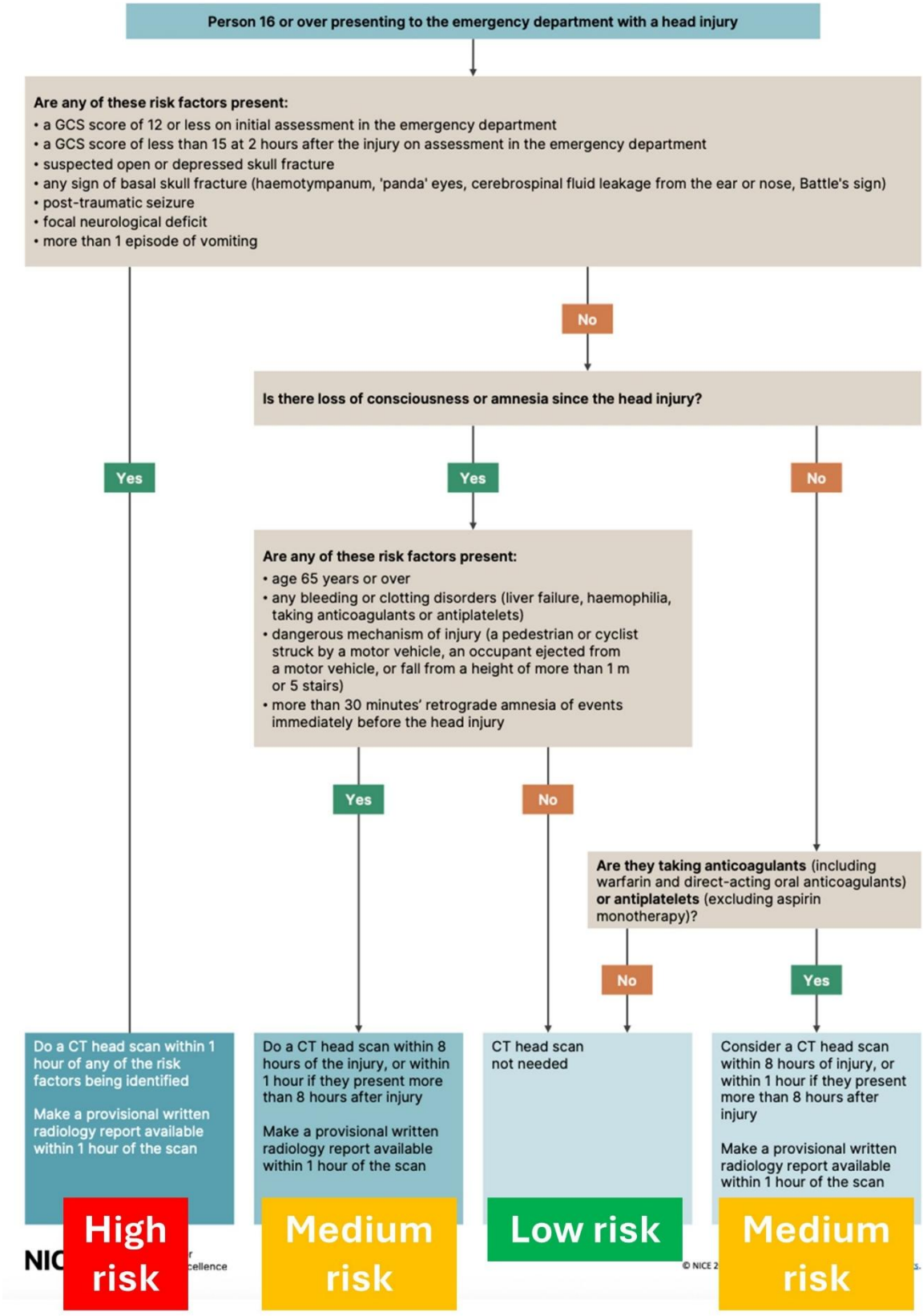

Please note that due to device regulations patients will only be recruited to BRAINS-TBI CT (nested RCT) if 18 years and over.

Patients aged 16 years and over are eligible for recruitment into BRAINS-TBI Cohort (Prognostic study)