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PROTOCOL SUMMARY

FULL TITLE OF STUDY	Intramuscular tranexamic acid for the treatment of symptomatic mild traumatic brain injury in older adults: a randomised, double-blind, placebo-controlled trial		
SHORT TITLE	Clinical Randomisation of Antifibrinolytic in Symptomatic mild Head injury in older adults		
TRIAL ACRONYM	CRASH-4		
SPONSOR'S ID NUMBER	2020-KEP-456		
EUDRACT NUMBER	2020-003391-40	**CLINICALTRIALS.GOV ID:**	NCT04521881

BACKGROUND: A fall from standing height in older adults is the commonest cause of major trauma in the UK. Traumatic brain injury (TBI) accounts for half of trauma admissions in older adults and is a leading cause of death and disability. Because the population aged over 70 years is increasing, the number of older adults with TBI will continue to rise. Most (90%) of the 1.4 million TBI patients seen each year in emergency departments in England and Wales have mild (Glasgow Coma Scale (GCS) score 13-15) head injury, but the term 'mild' is misleading in older adults who have higher death rates and worse outcomes than younger patients. Due to increased use of anticoagulant and antiplatelet drugs, older adults are more likely to suffer intracranial bleeding after mild TBI. TBI is also a strong risk factor for dementia in older adults.

Tranexamic acid (TXA) reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots. Results from randomised trials (CRASH-3 and NCT01990768) show that early treatment with TXA reduces head injury deaths (pooled RR 0.89, 95% CI 0.80-0.99). In the CRASH-3 trial, the reduction in head injury deaths with TXA was largest in patients with mild and moderate head injuries, particularly if patients were treated soon after injury. However, the CRASH-3 trial included mild TBI patients only if they had intracranial bleeding on CT scan. It is uncertain whether the results apply to mild TBI patients more generally.

Intracranial bleeding occurs soon after injury and early treatment is most effective. We have shown that TXA is rapidly absorbed after intramuscular injection in trauma patients without local side effects. This means that paramedics can give intramuscular TXA before transport to hospital, and for those who do not travel by ambulance, intramuscular TXA can be given immediately on hospital arrival. If early intramuscular TXA treatment reduces death and disability in older adults with mild TBI this would be a major medical advance that would improve the care of many millions of patients in the UK and world-wide.

AIM: The CRASH-4 trial aims to provide reliable evidence about the effects of early intramuscular TXA on intracranial haemorrhage, disability, death, and dementia in older adults with symptomatic mild head injury.

OBJECTIVES: To assess the effectiveness and safety of early intramuscular TXA administration in older adults with mild head injury. Outcomes include the proportion of patients discharged from the emergency department within 24 hours of arrival, intracranial bleeding on CT scan, neurosurgery, death due to intracranial bleeding and the risk of dementia at 1 year. Key safety outcomes include vascular occlusive

events, seizures, and pneumonia. The pilot phase will test all trial procedures and will also establish the impact of the SARS-CoV-2 pandemic on the trial. This will allow us to modify the procedures for recruitment and data collection for the main trial.

TRIAL DESIGN: A randomised, double blind, placebo-controlled trial in symptomatic mild TBI in about 10,000 older adults. The pilot phase will include about 500 patients.

ELIGIBILITY CRITERIA:

- 70 years or older (actual or estimated)
- History or evidence of head injury (e.g. laceration, bruise, swelling or pain in head or face)
- GCS ≥ 13
- Has one or more of the following:
  - has or had any impaired consciousness (loss of consciousness, amnesia, or confusion)
  - nausea or vomiting
- Within 3 hours of injury (do not include if interval cannot be estimated e.g. patient unable to confirm time of fall or patient found on floor after an unwitnessed fall and home alone)
- Not living in a nursing home, mental health institution or prison
- Patient will be conveyed to or is admitted to a participating hospital
- TXA not clearly indicated (e.g. major bleeding) or contraindicated (e.g. known allergic reaction or suspected acute arterial or venous thrombosis)
- Not known to have a diagnosis of dementia

TEST PRODUCT, REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION: Patients will be randomised to receive either 500mg TXA or matching placebo (a single 5mL IM injection of 100mg/ml or two x 2.5mL IM injections) as soon as possible after injury but no later than 3 hours, into the deltoid, thigh or buttocks depending on muscle mass.

DURATION OF TREATMENT AND PARTICIPATION: A dose of 500mg TXA will be given intramuscularly as soon as possible after randomisation. Outcome will be assessed in-hospital at discharge, death, or 28 days after randomisation, whichever occurs first. Where patients are discharged before day 28, readmission to hospital will be collected until day 28. Dementia diagnosis will be collected 1 year after randomisation from the HES dataset via NHS Digital. For recruited patients, the trial ends at death or 12 months after randomisation.

PRIMARY OUTCOME: The primary outcome is discharge from the emergency department within 24 hours of arrival.

SECONDARY OUTCOMES:

a. Intracranial bleeding on CT scan
b. Death (intracranial bleeding-related, other causes)
c. Disability (Barthel scale)
d. Global assessment of ability to selfcare functioning
e. Vascular occlusive events (pulmonary embolism, myocardial infarction, deep vein thrombosis, stroke)
f. Seizures
g. Pneumonia
h. Injection site reaction
i. Other adverse events

j. Patient management (neurosurgery, days in ICU, days in hospital)
k. Re-admission to hospital within 28 days
l. Dementia diagnosis at 1 year

SETTING: This trial will be conducted in ambulance services and emergency departments in the UK and coordinated from the Clinical Trials Unit, London School of Hygiene & Tropical Medicine.

CRITERIA FOR EVALUATION: All patients randomly assigned to one of the treatments will be analysed together, regardless of whether they completed or received that treatment or not, on an intention to treat basis.

CLINICAL PHASE	3		
PLANNED TRIAL START	01 June 2020	**PLANNED RECRUITMENT START**	01 November 2020
PLANNED DATE OF LAST PATIENT ENROLMENT	31 January 2025	**PLANNED DATE OF LAST OUTCOME**	28 February 2026