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PROTOCOL SUMMARY

FULL TITLE OF STUDY:	Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind placebo controlled trial		
SHORT TITLE:	Clinical randomisation of an antifibrinolytic in significant head injury		
TRIAL ACRONYM:	CRASH-3		
PROTOCOL NUMBER:	ISRCTN15088122		
EUDRACT NUMBER:	2011-003669-14	**CLINICALTRIALS.GOV ID:**	NCT01402882

BACKGROUND: Worldwide, over 10 million people are killed or hospitalised because of traumatic brain injury (TBI) each year. About 90% of deaths from TBI occur in low and middle income countries. TBI mostly affects young adults and many experience long lasting or permanent disability. The social and economic burden of TBI is considerable. Tranexamic acid (TXA) is commonly given to surgical patients to reduce bleeding and the need for blood transfusion. TXA has been shown to reduce the number of patients receiving a blood transfusion by about a third, reduces the volume of blood transfused by about one unit, and halves the need for further surgery to control bleeding in elective surgical patients. The CRASH-2 trial showed that administration of TXA significantly reduces deaths due to bleeding (RR=0.85, 95% CI 0.76–0.96; p=0.008), and all-cause mortality (RR=0.91, 95% CI 0.85–0.97; p=0.0035), with no increase in vascular occlusive events. A meta-analysis of randomised controlled trials of TXA in TBI showed a significant reduction in haemorrhage growth (RR=0.72; 95% CI 0.55–0.94) and mortality (RR=0.63; 95% CI 0.40–0.99) with TXA. Although the results from these trials are promising, the estimates are imprecise and there are no data on the effect of TXA on disability.

AIM: The CRASH-3 trial will provide reliable evidence about the effect of tranexamic acid on mortality and disability in patients with TBI. The effect of TXA on the risk of vascular occlusive events and seizures will also be assessed.

OUTCOME:

PRIMARY OUTCOME: The primary outcome is death in hospital within 28 days of injury among patients randomised within 3 hours of injury (cause of death will be described).

SECONDARY OUTCOMES:

(a) Vascular occlusive events (myocardial infarction, pulmonary embolism, clinical evidence of deep vein thrombosis)
(b) Stroke
(c) In hospital disability assessed using the Disability Rating Scale and Patient Orientated Outcome
(d) Seizures
(e) Neurosurgical intervention
(f) Days in intensive care
(g) Other adverse events

TRIAL DESIGN: A pragmatic, randomised, double blind, placebo controlled trial among 13,000 traumatic brain injury patients

DIAGNOSIS AND INCLUSION/EXCLUSION CRITERIA:

Adults with traumatic brain injury who

- are within eight hours of injury (for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury)
- with any intracranial bleeding on CT scan or who have a GCS of 12 or less, and
- have no significant extracranial bleeding (needing immediate blood transfusion)

The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use tranexamic acid in a particular patient with traumatic brain injury.

TEST PRODUCT, REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION: A loading dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) will be given as soon as possible after randomisation. A maintenance dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) will be given after the loading dose is finished.

SETTING: This trial will be coordinated from the London School of Hygiene & Tropical Medicine (University of London) and conducted worldwide in hospitals in low, middle and high income countries.

DURATION OF TREATMENT AND PARTICIPATION: The loading dose will be given as soon as possible after randomisation and the maintenance dose will be given immediately after the loading dose over 8 hours.

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

CLINICAL PHASE	3		
PLANNED TRIAL START	01 December 2011		
PLANNED DATE OF LAST PATIENT ENROLMENT	31 January 2019	**PLANNED DATE OF LAST OUTCOME**	28 February 2019