Tranexamic acid for hyperacute spontaneous IntraCerebral Haemorrhage (TICH-3)

Final Version 3.0 28/02/2024

Short title: **Tranexamic acid for IntraCerebral Haemorrhage**

Acronym: **TICH-3**

EudraCT number: **2021-001050-62**

EU CTIS registration number: - 2022-500587-35-00

Trial Registration: **ISRCTN97695350**

CTA reference: 03057/0074/001-0001

IRAS Project ID: **297457**

Trial Sponsor: University of Nottingham

Sponsor reference: **21022**

Funding Source: **NIHR HTA Project grant NIHR129917** (Lerdal & Kottorp, 2011)

TRIAL / STUDY PERSONNEL AND CONTACT DETAILS

Sponsor:
Contact name

University of Nottingham
Mr Ali Alshukry
Head of Research Integrity, Governance & Compliance
Research and Innovation
E Floor, Yang Fujia, Jubilee Campus
The University of Nottingham
Wollaton Road
Nottingham
NG8 1BB
Telephone: +44 (0) 115 74 85224
Mobile: +44 (0) 7866 137607
Email: sponsor@nottingham.ac.uk

Chief investigator:

Professor Nikola Sprigg
Professor of Stroke Medicine
University of Nottingham
Phone: 0115 8231765

Email: nikola.sprigg@nottingham.ac.uk

Co-investigators:
(Medical Expert)

Professor Philip Bath
Stroke Association Professor of Stroke Medicine
University of Nottingham
Phone: 0115 8231765

Email: philip.bath@nottingham.ac.uk

Professor Rob Dineen
Professor of Neuroimaging
University of Nottingham
Phone: 0115 82 31173
Email: rob.dineen@nottingham.ac.uk

Dr Michael Desborough
Academic Clinical Lecturer
Oxford University Hospitals
Phone: 01865 447900
Email: michael.desborough@ouh.nhs.uk

Professor Ian Roberts
Professor of Epidemiology & Public Health
London School of Hygiene & Tropical Medicine
Phone: 020 7299 4684
Email: ctu@lshtm.ac.uk

Professor Alan Montgomery
Professor of Medical Statistics and Clinical Trials
NCTU Director
Clinical Trials Unit
University of Nottingham
Phone: 0115 8231612
Email: alan.montgomery@nottingham.ac.uk

Professor Rustam Al-Shahi Salman
Professor of Clinical Neurology
University of Edinburgh
Phone: 0131 242 7014
Email: Rustam.al-shahi@ed.ac.uk

Professor Christine Roffe
Consultant Stroke Physician
University Hospitals of North Midlands NHS Trust
Phone: 01782 671655
Email: Christine.roffe@uhnm.nhs.uk

Professor David Werring
Professor of Clinical Neurology
UCL Institute of Neurology
Phone: 020 3108 7493
Email: d.werring@ucl.ac.uk

Associate Professor Timothy England
Clinical Associate Professor, Vascular Medicine
University of Nottingham
Phone: 01332 724668
Email: timothy.england@ottingham.ac.uk

Professor Timothy Coats
Professor of Emergency Medicine
University of Leicester
Phone: 0116 2585965
Email: tc61@le.ac.uk

Professor Marilyn James
Professor of Health Economics
University of Nottingham
Phone: 0115 8230245

	Email: Marilyn.james@nottingham.ac.uk Associate Professor Caroline Rick Associate Professor of Methodology Nottingham Clinical Trials Unit University of Nottingham Phone: 0115 8231600 Email: caroline.rick@nottingham.ac.uk Professor Thompson G Robinson Professor of Stroke Medicine University of Leicester Phone: 0116 2522961 Email: tgr2@le.ac.uk
Trial / Study Statistician: (and co-applicant)	Trish Hepburn Phone: 0115 8231561 Email trish.hepburn@nottingham.ac.uk
Trial Pharmacist:	Cherrelle Evans Phone: TBC Email cherrelle.evans@nuh.nhs.uk
Trial Coordinating Centre: Centre:	Stroke Trials Unit University of Nottingham Phone: 0115 8231782 Email: TICH-3@nottingham.ac.uk
Project / Trial Manager:	Tiffany Hamilton Phone: 0115 8231775 Email tiffany.hamilton@nottingham.ac.uk
Legal Representative in European Union:	Project Manager Katrina Tobin Director Prof Peter Kelly HRB Stroke Clinical Trials Network, Ireland UCD Clinical Research Centre Nelson Street, Dublin 7, Ireland Tel: +353 1 716 4576

SYNOPSIS

Title	Tranexamic acid for Hyperacute Spontaneous Intracerebral Haemorrhage (TICH-3)
Acronym	TICH-3
Short title	Tranexamic acid for Hyperacute Spontaneous Intracerebral Haemorrhage
Chief Investigator	Professor Nikola Sprigg
Objectives	To assess the clinical effectiveness of tranexamic acid (TXA) after ICH and determine whether TXA should be used in clinical practice. Primary objective: To assess the effect of TXA on early death (≤7days) Secondary objective: To assess the effect of TXA on dependency 6 months after ICH.
Trial Configuration	Pragmatic phase III prospective blinded randomised placebo-controlled trial.
Setting	Emergency departments, acute stroke services/units across the UK and worldwide.
Sample size estimate	2750 participants per group would allow detection of a difference of 2.57% in the proportion of deaths at day 7 between the placebo and TXA groups (7.74% deaths on TXA, OR of 0.73), at the 5% significance level (2-sided) with 90% power. As the primary outcome is death we anticipate there will be minimal loss to follow up.
Number of participants	At least 5500
Eligibility criteria	**Inclusion criteria:** Adults (≥ 18 years) within 4.5 h of onset of acute spontaneous ICH (confirmed on brain imaging). When onset of symptoms is unknown patient must be within 4.5 hours of symptom discovery and have no other exclusion criteria. **Exclusion Criteria**: i. Patient with a known indication for TXA treatment (e.g. traumatic brain injury). ii. Patient with contraindication for TXA treatment iii. Patient known to be taking therapeutic anticoagulation with warfarin or low molecular weight heparin at time of enrolment. Patients taking direct oral anticoagulants can be included and are not excluded. iv. Massive ICH for which haemostatic treatment seems futile (This would ordinarily be when haematoma volume is estimated as larger than 60ml) v. Severe coma (Glasgow Coma Scale <5) vi. Decision already taken for palliative (end of life) care with withdrawal of active treatment
Description of interventions	Intravenous TXA 2g: 1g loading dose given as 100 mls infusion over 10 minutes, followed by 1g in 250 mls infused over 8 hours. Comparator – matching placebo (normal saline 0.9%) administered by an identical regimen.
Duration of study	7.25 years project; approximately 5.25 years participant recruitment in the UK, 4.75 years in international sites, Start date 1 April 2022 Duration of study per participant: 6 months.

Randomisation and blinding	Randomisation will be to TXA vs. placebo in a 1:1 ratio. Due to the emergency situation, a straightforward randomisation process will be used, where sites will simply open the next available lowest numbered treatment pack, which will be a numbered box containing either TXA or placebo according to a computer-defined sequence. Boxes will be identical with the exception of the treatment pack number. Randomisation will be stratified by site with supply to each site balanced for TXA and placebo, using random permuted blocks of varying size. The IMP manufacturer will prepare blinded individual treatment packs containing four 5ml glass ampoules of TXA 500mg or sodium chloride 0.9% which will be very similar in appearance.
Outcome measures	**Primary outcome:** mortality at 7 days, Secondary functional outcome: modified Rankin Scale at (mRS) 180 days. Other secondary outcomes: Death at 2 days. Safety outcomes**:** Recorded in the first 7 days (or death if sooner): venous thromboembolism; ischaemic events (arterial thrombosis at any site, ischaemic stroke, transient ischaemic attack peripheral artery embolism, myocardial infarction, acute coronary syndrome); seizures. Quality of Life (EuroQol(Devlin et al., 2018), EQ-5D-5L, VAS), and cognition (AD-8)(Galvin et al., 2007) at day 180. Fatigue severity scale (Lerdal & Kottorp, 2011).
Resource and Cost Measures	Hospital resource and cost at discharge, to include: length of stay, days in ICU and treatments. Usual residence: Disposition at discharge and day 180. Patient level Health Resource Use Questionnaire at day 180.
Statistical methods	The analysis and presentation of the trial results will be in accordance with the CONSORT guidelines. The primary outcome will be compared analysing as randomised without imputation of missing data. Due emphasis will be placed on the confidence intervals for the between arm comparisons. A full Statistical Analysis Plan (SAP) will be developed prior to database lock. The evaluation of the primary outcome will be performed using regression models for binary outcomes, with adjustment for key prognostic factors. The model will be fully specified in the SAP. Absolute and relative measures of effect and 95% confidence intervals will be presented. The primary outcome will also be investigated in pre-specified subgroups using appropriate interaction terms. The subgroups will be specified in the SAP and will, at a minimum include age, sex, systolic blood pressure, HV, GCS, the start of treatment (≤2 or >2 hours, ≤3 or >3 hours), antiplatelet (yes no), direct oral anticoagulation (DOAC) (yes, no) and intraventricular haemorrhage (yes, no).
Health Economic Analysis	Cost effectiveness of TXA versus usual care. Incremental cost effectiveness ratios (ICERs), net monetary benefit and cost effectiveness of usual care versus TXA
Simplicity of Trial Procedures	To reflect the time critical emergency nature of ICH, and to facilitate rapid enrolment in emergency departments, patient enrolment (simple randomisation) and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal. Randomisation via opening the next lowest numbered treatment pack is simple and quick. Follow-up information is recorded at a single timepoint and may be

	ascertained by contacting participants, by post, phone or electronically, or by review of medical records and databases.

ABBREVIATIONS

ACS	Acute coronary syndrome
ADR	Adverse Drug Reaction
AD-8™	Cognition measure
AE	Adverse Event
BP	Blood pressure
CF	Informed Consent Form
CI	Chief Investigator overall
CEA	Cost Effectiveness Analysis
CUA	Cost Utility Analysis
ICER	Incremental Cost Effectiveness Ratio
CEAC	Cost Effectiveness Acceptability Curves
NMB	Net Monetary Benefit
CRF	Case Report Form
CT	Computed tomogram
CTA	Computed tomogram angiogram
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
DOAC	Direct Oral Anticoagulation
DNACPR	Do not attempt cardiopulmonary resuscitation
DVT	Deep vein thrombosis
EOT	End of Trial
EQ-5D™	EuroQol 5-Dimension 5-Level quality of life assessment tool
GCP	Good Clinical Practice
HG	Haematoma growth
HEE	Health economic evaluation
HV	Haematoma volume
ICH	Intracerebral haemorrhage
IS	Ischaemic stroke
NIHR	National Institute for Health Research
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
NHS	National Health Service
mRS	modified Rankin Scale
NIHSS	National Institutes for Health Stroke Scale
PE	Pulmonary embolism
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study within a trial
TBI	Traumatic brain injury
TMG	Trial Management Group
TSC	Trial Steering Committee
TXA	Tranexamic acid
VAS	Visual analogue scale
VTE	Venous thromboembolism

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

ICH is a medical emergency and causes more than 1.7 million strokes worldwide per year(Feigin et al., 2009; O'Donnell M.; Venketasubramanian N.; Baker-Collo S.; Lawes CMM.; Wang W.; Shinohara Y.; Witt E.; Ezzati M.; Murray C., 2013) with a mortality of over 40%.(Flaherty et al., 2006) More than 10,000 people suffered an ICH last year in England. There is no effective drug treatment for ICH, and only a small proportion of patients benefit from surgery. Haematoma growth is common, occurs early,(Brott et al., 1997; Davis et al., 2006) and is the most common cause of death after ICH. It can potentially be prevented by haemostatic therapies, which are effective in other bleeding conditions.(Collaborators, 2010; WOMAN Trial Collaborators, 2017)
Time from symptom onset, baseline haematoma growth and anti-thrombotic therapy use are all independent predictors of haematoma growth.(Al-Shahi Salman et al., 2018) The Computed Tomography (CT) spot sign can also improve the prediction model but has not been successful in previous trials(Gladstone et al., 2019) and is not routinely performed in clinical practice.

ICH related disability causes massive burdens to the affected individual, their family and society. ICH was identified as a priority research area by The Stroke Association, with interventions to stop bleeding as a treatment target.(*https://www.stroke.org.uk/news/haemorrhagic-stroke-workshop-priority-setting*, 2014) The incidence of ICH is increasing due to high blood pressure and the ageing population, with ICH-related death and disability set to rise.(Feigin V et al., 2013; Kleindorfer et al., 2010) Recent improvements in stroke pathways have led to rapid imaging, with early diagnosis providing an opportunity to rapidly administer treatments. Implementation of an effective haemostatic therapy such as TXA is therefore possible in ICH.
The proposed study will build on experience from the NIHR HTA funded TICH-2 trial,(Sprigg et al., 2018) streamline trial methods and enable rapid enrolment of those most likely to benefit. If the haemostatic effect demonstrated in TICH-2 (with reduction in early death) is confirmed in TICH-3, this could change clinical practice globally. By enrolling participants earlier and excluding those with established large HVs, TICH-3 targets patients with the greatest potential to benefit.

Review of existing evidence: TXA in other bleeding conditions
TXA is an antifibrinolytic agent licensed for perioperative use. It reduces mortality after trauma and childbirth and is most effective when given rapidly after the onset of bleeding.(Gayet-Ageron et al., 2018). The CRASH 3 RCT("Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial," 2019) of TXA in traumatic brain injury has been published since submission of stage 1 application: TXA was safe in 12737 participants with traumatic brain injury. Overall, there was a reduction in day 30 head injury related mortality (Risk reduction RR 0.94; 95%CI 0.86-1.02), in a pre-specified sensitivity analysis excluding very severe head injury (RR 0.89; 95%CI 0.80-1.0), and benefit in mild-moderate head injury deaths (RR 0.78; 95%CI 0.64-0.95). The effect size was greater when early death (< 24 hours) was the outcome RR 0.81 (95% CI 0.69–0. 95) within 24 h. When patients with a GCS score of 3 and those with bilateral unreactive pupils at baseline were excluded, the RR was 0.72 (0.56–0.92).
Rapid treatment was the most effective in mild-moderate head injury, with some benefit up to 4.5 hours. There was no benefit in patients with severe coma score, irrelevant of time.
Summary of TXA data in non-ICH patients: TXA is effective at reducing mortality due to bleeding after trauma, post-partum haemorrhage and traumatic brain injury. Treatment is most effective when given early and the effect is greatest on early mortality. A number of differences in patient population, pathophysiology and natural history mean these results cannot simply be translated to ICH patients.

TXA after intracerebral haemorrhage (ICH):

Observational studies: 2 small observational studies of TXA after ICH have been reported. Sorimachi et al. reported a retrospective observational before–after study comparing the efficacy of rapid infusion of TXA 2 g over 10 min to prolonged infusion of 1 g over 6 h in patients presenting within 24 h of ICH. The study recruited 156 patients (>80% presented within 3 h of onset) and showed that rapid infusion was associated with less haematoma enlargement of >20% than prolonged infusion (17.5% vs. 4.3%, $p = 0.011$).[27] The authors subsequently reported a study of additional 95 patients treated with rapid infusion of TXA with HE occurring in 4.2% of these patients.[28] However, there was no control arm in either study.
Ojacastro et al. reported an observational study of 30 patients aged 40–70 years with hypertensive ICH who received either intravenous TXA 500 mg for three doses or standard care. The study is reported as an abstract only, with no data other than a general statement of HV reduction with TXA without effect on length of stay or in-hospital National Institute of Health Stroke Scale (NIHSS).[29]

Randomised controlled trials of TXA after ICH:
A systematic review in 2018 was inconclusive about the safety and efficacy of antifibrinolytics after ICH as there were only 2 published randomised controlled trials (RCTs) with a total of 57 participants.(Rustam Al-Shahi Salman et al., 2018) 3 other studies were on-going and one TICH-2 (lead by this group) reported in 2018.The results of the completed RCTs and summary of on-going trials are presented below. The majority of studies use the radiological endpoint haematoma expansion (HE) as a surrogate outcome measure, to demonstrate haemostasis. Dependency assessed by modified Rankin Scale is the most frequently used functional outcome.

Randomised controlled trials n=<100 participants:
The TXA in IntraCerebral Haemorrhage (TICH) trial(Sprigg et al., 2014) recruited 24 patients within 24 h of ICH to receive either 1 g TXA or placebo over 10 min followed by 1 g over 8 h. This trial was designed as a feasibility trial and not to investigate efficacy.
Arumugam et al.(Arumugam et al., 2015) conducted a single-centre, single-blind RCT that allocated 30 patients to receive within 8 h of ICH either intravenous TXA 1 g over 10 min followed by 1 g over 8 h or placebo. Participants in the control group experienced more haematoma expansion compared to the treatment group. The mean Glasgow Outcome Scale score was 3.6 in the control group and 4.4 in the treatment group, but no estimated between group difference was provided.
The Norwegian Intracerebral Haemorrhage Trial (NOR-ICH, EudraCT number 2012-005594-30) was a multicentre prospective randomised, open-label, blinded endpoint (PROBE) trial. The study has terminated early due to problems with recruitment and has not been published. Approximately 30 participants were enrolled.

Tranexamic acid for Hyperacute Spontaneous Intracerebral Haemorrhage-2: Most of the data on TXA in ICH come from TICH-2(Sprigg et al., 2018) (n=2325, treatment within 8 hours of ICH, delivered by the co-applicants) which showed that TXA was safe, led to reduction in HE (adjusted odds ratio (aOR) 0.80; 95%CI 0.66-0.98, p=0.03) and reduction in early day 7 deaths (aOR 0.73; 95%CI 0.53-0.99; p=0.04), but no difference in functional outcome of modified Rankin Scale at 3 months (aOR 0.88; 95%CI 0.76-1.08).(Sprigg et al., 2018) In keeping with data from CRASH-3 in TBI, the effect on early mortality was greater: day 2 OR (aOR 0.61 95% CI 0.38 - 0.98 p=0.04). In a UK sub-study, (n=1873) following patients up to one year, there was no difference in functional outcome using a shift analysis (aOR 95% 0.91 CI: 0.77-1.09; p=0.30) but there was difference in cumulative mortality (cox proportional hazard analysis) (aHR 0.77, 95% CI 0.64-0.94; p=0.0086). There was also a trend for participants in the TXA group to have better discharge disposition and less likely to be in an institution.
Interpretation of data from TICH-2: Inclusion of participants too late after ICH, when HE had already occurred and a more modest haemostatic effect than expected are likely to explain the neutral primary outcome of TICH-2.(Broderick, 2018) Treatment effect was possibly diluted by

inclusion of patients with large HV already pre-destined to a bad outcome. Hence TXA is still considered a viable treatment option (Cordonnier et al., 2018) and studies with a shorter time window are needed.(Donnan, 2019) Participants enrolled within 4.5 h in TICH-2 had a reduction in poor functional outcome (aOR 0.84; 95%CI 0.70-1.01). Furthermore an *ad hoc* analysis of 1377 participants with small haematomas (<60 ml) enrolled early (within 4.5 h) suggested possible reduction in early death by day 7 (aOR 0.70; 95%CI 0.43-1.15; p=0.15).

Evidence from other ICH studies:
Three RCT have recently completed and another is ongoing: Details are given below but these are all small studies with radiological measures as primary outcome and therefore unlikely to change practice, even as part of a planned prospective individual patient data meta-analysis.(Zhe Kang Law, 2017)

The Spot sign and TXA On Preventing ICH growth – AUStralasia Trial STOP-AUST (NCT01702636) was a phase-II multicentre randomised, double-blind, placebo-controlled trial exploring the efficacy of TXA in preventing HE in ICH patients, recruiting patients from Australia, Finland and Taiwan.[32]The trial selected patients with a positive spot sign on CT angiography to receive either placebo or 1 g TXA over 10 min followed by 1 g over 8 h. The primary outcome measure was HE by 24 h, with mRS and thromboembolic complications at 90 days as secondary outcomes. They recruited a total of 100 participants The primary outcome was not different between the two groups: 26 (52%) patients in the placebo group and 22 (44%) in the TXA group had intracerebral haemorrhage growth (odds ratio [OR] 0·72 [95% CI 0·32-1·59], p=0·41). There was no evidence of a difference in the proportions of patients who died or had thromboembolic complications between the group.(Meretoja et al., 2020)

TXA for Acute ICH Growth prEdicted by Spot Sign TRAIGE (NCT02625948) is a multicentre phase-II randomised, double blind, placebo-controlled trial recruiting patients from China who have a positive spot sign on CT angiography and can be treated within 8 h from onset. The trial compared the efficacy of intravenous TXA followed by intravenous TXA 1 g infusion over 8 h versus placebo. The primary outcome measure is HE by 24 h, with mRS and thromboembolic complications at 90 days as secondary outcomes. The trial recently completed recruitment of 171 participants and results did not differ significantly between the two groups: 36 (40.4%) patients in the TXA group and 34 (41.5%) patients in the placebo group had intracranial haemorrhage growth (OR 0.96, 95% CI 0.52 to 1.77, p=0.89). Although in the secondary outcome analysis the TXA group had lower 90 day mortality compared to placebo (8.1% vs 10.0%, p=0.71), all of the secondary outcomes were statistically insignificant.(Liu et al., 2021)

TXA for IntraCerebral Haemorrhage secondary to Novel Oral AntiCoagulants TICH-NOAC was a multicentre international double-blind placebo-controlled trial, investigating the safety and efficacy of TXA in ICH related to non–vitamin K (direct) oral anticoagulants (NOAC). The time window for recruitment is up to 12 h after the onset of ICH. Patients are randomised to receive TXA 1 g bolus followed by 1 g infusion over 8 h or Placebo. All patients receive standard treatment including specific antidote where available. TICH-NOAC aims to demonstrate that treatment with TXA reduces rate of HE as measured at 24 h compared to the best medical treatment. The trial randomized 63 patients within 12 hours of symptom onset and treated them with TXA or placebo within 30 minutes of randomization. There was no evidence that TXA (1g bolus then 1g infusion) prevents hematoma expansion, with rates of almost 50% in both arms. Rates of severe disability and death were also comparable in the treatment and placebo arms. Prespecified subgroup

analyses identified several factors associated with the effect of TXA on hematoma expansion, including time-to-treatment and blood pressure (Polymeris et al., 2023).

Stopping Haemorrhage with TXA for Hyperacute Onset Presentation Including Mobile Stroke Units STOP-MSU **(**NCT03385928) was presented at the World Stroke Conferece 2023. It included patients from Australia with acute spontaneous ICH, who are ≥18 years of age and are eligible for treatment within 2 hours of stroke onset. The study tested the hypothesis that intracranial haemorrhage patients treated with intravenous TXA within 2 hours of symptom onset will have lower rates of HE as compared to placebo. The study showed that TXA had a goos safety profile and we await the full publication (Yassi et al., 2022).

On-going trials:
Pandian et al, the INTRINSIC (NCT05836831). A randomised, open control trial for patients presenting with spontaneous intracerebral haemorrhage within 4.5 hours in India. Aiming to recruit 3400 patients.

Jiang et al, the ICH-trial (ChiCTR1900027065)). A randomised placebo controlled double blind study for patients presenting with spontaneous intracerebral haemorrhage within 4.5 hours in China. Aiming to recruit 2400 patient.

Recent metanalyses looking at the safety of TXA in ICH:
A recent Cochrane review has been updated 'Haemostatic therapies for acute, spontaneous intracerebral haemorrhage'. In summary there are currently no haemostatic treatments that improve mortality or morbidity. Looking at tranexamic acid in particular, tranexamic acid did not show any safety concerns compared to placebo and TXA favoured reduction in haematoma volume compared to placebo (Eilertsen et al., 2023).

Conclusion: More high-quality data from large RCTs in ICH are urgently needed, particularly in patients soon after ICH onset, when the risk of haematoma a growth is highest and the potential benefit from TXA greatest. Evidence of benefit on clinical outcomes (rather than radiological surrogate measures such as HE) in ICH is necessary to change practice in stroke services in the UK and worldwide.

DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Description and Manufacture

Intravenous tranexamic acid or matched placebo of intravenous Sodium Chloride 0.9% 5ml ampoules.

Tranexamic acid 100mg/ml 5ml ampoules are a licensed product and an example summary of the product characteristics is available for investigators.

Packaging and labelling

Sharp Clinical Services Ltd will prepare blinded individual treatment packs containing four 5ml glass ampoules of tranexamic acid 500mg or sodium chloride 0.9% which will be very similar in appearance by the addition of a heat shrink sleeving. Ampoules and the secondary carton will be labelled in accordance with Annex 13 of Volume 4 of The Rules Governing Medicinal Products in the EU: Good Manufacturing Practices, assuming that the primary and secondary packaging remain together throughout the trial. To facilitate identification the carton and the ampoules contained within it will be labelled with the same unique pack number.

Detailed prescribing and administration instructions will be provided in the treatment pack.

The final product will be QP released by the designated person at Sharp Clinical Services to provide blinded trial treatment packs for this trial.

Storage, dispensing and return

Sharp Clinical Services Ltd will store the treatment packs and distribute to pharmacies within trial sites using a web-based system control. Pharmacy at each participating site will take receipt of numbered supplies from Sharp Clinical Services.

The web-based system operates as follows. Participating centres will be allocated a batch of trial treatment. The container numbers for these batches are tracked by the web-based system to the participating site and once receipt has been confirmed they are released for use in the trial. When the supplies at the participating centre reach a pre-determined level then a re-order is triggered, and a further supply of trial treatment is sent to the corresponding participating site.

The packs will be stored at room temperature and protected from excessive heat and freezing in a restricted access area. Stability data exists which demonstrates that TXA is stable at temperatures between -20°C and 50°C. (de Guzman R, 2013) Temperature monitoring will not be required. The IMP will be clearly labelled for clinical trial use only. Each pack will be a numbered box containing either TXA or placebo according to a computer-defined sequence.

The local site investigator is responsible for ensuring trial treatment accountability, including reconciliation of trial treatment and maintenance of trial treatment records, throughout the course of the study in accordance with UK regulatory requirements. Responsibility can be delegated to the site pharmacy clinical trials staff in accordance with local process.

Following enrolment personnel at sites will simply open the next available lowest numbered treatment pack, which will be a numbered box containing either TXA or placebo according to a computer-defined sequence. Boxes will be identical with the exception of the treatment pack number.
The participant will subsequently be allocated a participant trial number based on the treatment pack number when the treatment pack number is entered to the electronic case report form.

Prescription: The treatment will be prescribed by appropriately trained medical practitioners or health care professionals who are non-medical supplementary or independent prescribers. *It is acceptable to use handwritten or electronic prescribing system for IMPs prescribing.*

Dispensing will be recorded on the appropriate trial specific accountability forms. Trial treatment must not be used for any other purpose than the present study. Returned trial treatment that has been dispensed to a participant must not be re-dispensed to a different participant. Any unused drug will be returned to pharmacy.

Placebo

The placebo will be supplied, packaged, labelled, QP released and distributed as for the active IMP.

Known Side Effects

Gastrointestinal disorders (nausea, vomiting, diarrhoea) may occur but disappear when the dosage is reduced. Hypotension has occasionally been reported after rapid intravenous infusion. Rare instances of colour vision disturbances have been reported following long-term use. Rare cases of thromboembolic events have been reported. Rare cases of allergic skin reactions have also been reported.

TXA will counteract the thrombolytic effect of fibrinolytic preparations, but these would be contra-indicated in patients with haemorrhagic stroke.

Reference Safety Information:

Example Tranexamic Acid SmPC: https://stroke.nottingham.ac.uk/docs/TICH-3/MHRA_documents/TICH-3 Focus Tranexamic Acid 100mg ml Solution for Injection Summary of Product Characteristics %28SmPC%29 20210202 REVISION.pdf

Section 4.8 of the SmPC, date of last revision 02 February 2021, will act as the reference safety information.

Example Sodium Chloride SmPC: https://stroke.nottingham.ac.uk/docs/TICH-3/MHRA_documents/TICH-3%20Sodium%20Chloride%20Injection%20BP%200.9%20percent%20w%20v%20Summary%20of%20Product%20Characteristics%20%28SmPC%29.pdf

Section 4.8 of the SmPC, date of last revision 01 April 2020, will act as the reference safety information.

Drug accountability

Intracerebral haemorrhage is a medical emergency. The trial has been designed to embed within the clinical pathway for hyperacute stroke, such that hyperacute stroke patients are assessed immediately on arrival to hospital and urgent brain imaging performed to exclude haemorrhage, to allow thrombolysis to be given to patients with ischaemic stroke. Patients who have ICH confirmed on brain imaging will be offered participation in TICH-3. Unless they disagree to participate the IMP will be administered, and written consent taken later. As such the IMP needs to be available for immediate administration once the diagnosis of ICH has been confirmed. If the IMP has been opened and no diagnosis of ICH has been confirmed, the IMP will be destroyed according to local procedures. Hence it may be useful to take the IMP with the patient to the scanner, as is done with thrombolysis drugs, often as part of a ‘thrombolysis kit or grab bag’. The eligibility checklist and trial documentation should be kept in the ‘grab bag’ in the scenario that the research team are not available, the doctor treating the patient can assess eligibility and explain the trial to the participant/their relative. The IMP is clearly labelled for clinical trial use only. The remainder of the drug supplies will be kept in a secure, limited access storage area.

The investigator and the local site pharmacist shall maintain records of the study drug's delivery to the pharmacy, an inventory at the site, the distribution to each participant, and the return to the pharmacy or alternative disposition of unused study drugs. These records will include dates, quantities received, batch / serial numbers, expiration dates, and the unique code numbers (patient trial number) assigned to the trial participant. Investigators and /or the local site pharmacists will maintain records that document adequately that the participants were provided with the correct study medication. These records will be part of each patient's Case Report Form (CRF). All study medication packs received by the pharmacy shall be accounted for.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

To assess the clinical effectiveness of TXA after ICH. The results will determine whether TXA should be used in clinical practice to treat ICH.
Hypothesis: TXA improves outcome after ICH by stopping haematoma expansion, preventing early death and improving functional status in survivors.

PRIMARY OBJECTIVE

To assess the effect of TXA versus usual care on early death ≤7days after ICH.

SECONDARY OBJECTIVES

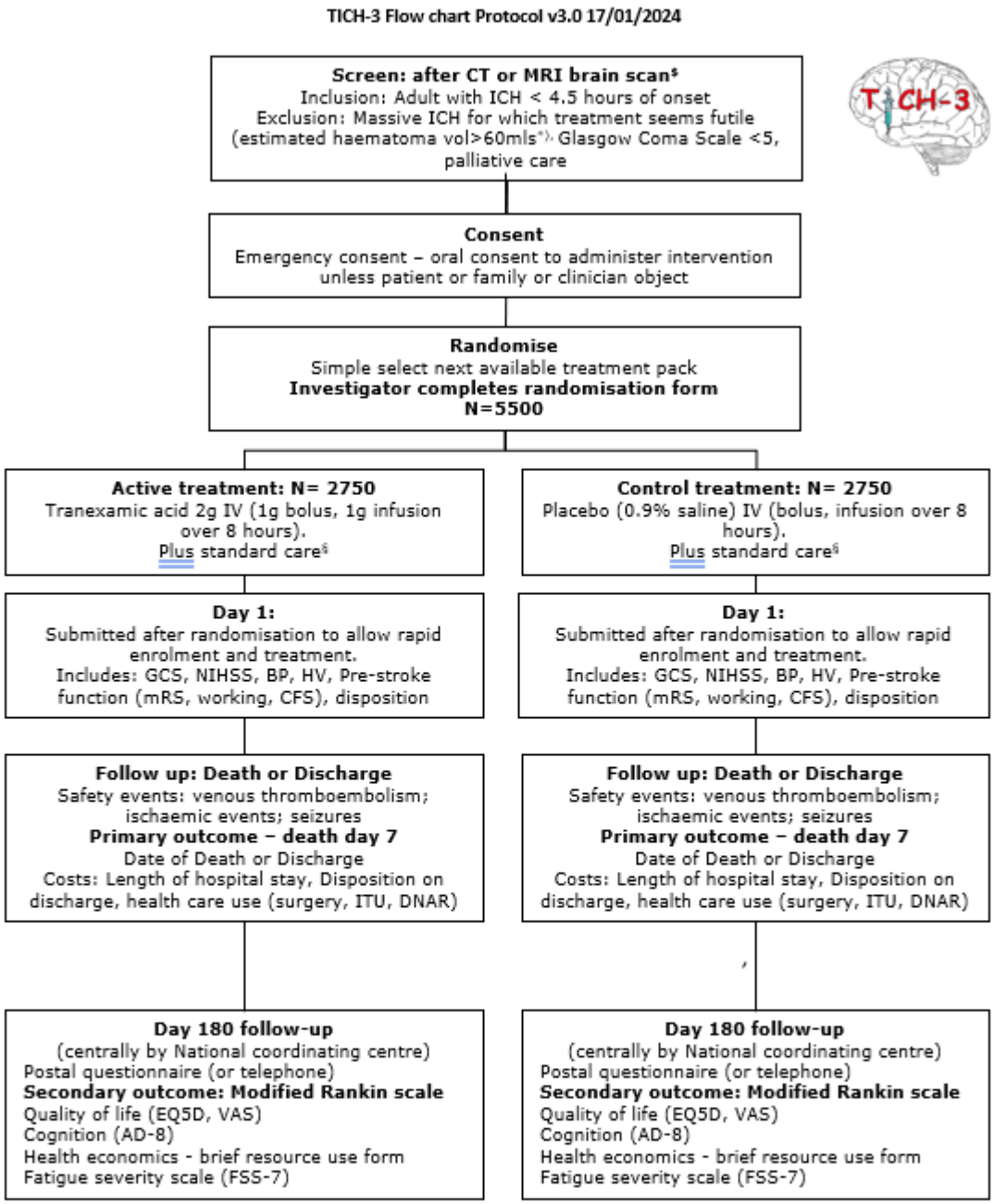
To assess the effect of TXA versus usual care on dependency (modified Rankin Scale) at day 180 after ICH.
To assess the cost effectiveness and cost utility (based on discharge and destination) of TXA versus usual care at day 180 after ICH.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

Pragmatic phase III prospective blinded randomised placebo-controlled trial performed in two phases: a 30-month internal pilot phase with pre-specified progression criteria then main phase (approximately 145 centres, recruit to a total of 5500 participants).
There will be no break in recruitment as the trial proceeds from the start-up phase to the main phase unless the pre-specified stopping criteria are met.
Appendix 1 shows a schematic diagram of trial design, procedures and stages, randomisation, baseline & intermediate visits, final visit, and long-term follow-up.

TRIAL FLOW CHART



Simplicity of Trial Procedures

To reflect the time critical emergency nature of ICH, and to facilitate rapid enrolment in emergency departments, patient enrolment (simple randomisation) and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal. Randomisation via opening the next lowest numbered treatment pack is simple and quick. Follow-up information is recorded at a single timepoint and may be ascertained by contacting participants, by post, phone, electronically, or by review of medical records and databases.

Primary Endpoint

Primary outcome:
Early death up to and including day 7 after ICH onset.

Justification of primary outcome: Functional outcome using the mRS at 90 days is the recommended outcome measure after stroke. However, our hypothesis is that TXA improves outcome by stopping HE. HE is the most common cause of early death after ICH, TXA is a haemostatic therapy, therefore we believe early mortality ≤7 days is the most appropriate outcome for TICH-3.

Secondary endpoint

Pre-specified secondary endpoint of importance: functional outcome: Dependency assessed by modified Rankin Scale (Sulter et al., 1999) at 180 days

Other secondary outcomes:

Safety endpoints

Recorded in the first 7 days (or death if sooner): venous thromboembolism; ischaemic events (arterial thrombosis at any site, ischaemic stroke, transient ischaemic attack, peripheral artery embolism, myocardial infarction, acute coronary syndrome) and seizures. All fatal events until discharge from hospital will be collected.

Secondary outcomes at 2 days
1. Death up to and including Day 2 after ICH onset

Secondary outcomes at 180 days
1. Functional status (mRS)
2. Quality of life (EQ-5D™)
3. Home time (no of days spent at home rather than in hospital or an institution)
4. Cognition (AD-8)(Galvin et al., 2007)
5. Fatigue Severity Scale (FSS-7) (Lerdal & Kottorp, 2011)

Health economic Data at Discharge

These will include the following to full evaluate all costs and outcomes associated with the inpatient stay
1. Antihypertensive therapy
2. Do not attempt resuscitation orders (DNAR),
3. Admission to intensive care unit,
4. Neurosurgical intervention,
5. Hospital length of stay,
6. Discharge disposition.
7. Eq5d

Health economic Data at 6 months

1. Readmissions,

2. Institutionalization
3. Days at home
4. Health and social use using brief patient data proforma (particularly in community, social care and primary care use)
5. Eq5d

Stopping rules and discontinuation

Participants may withdraw consent for treatment or follow up at any time. Study medication may be stopped at any time by the investigator or treating physician if deemed advisable, however the study medication is only administered for the first 8 hours of the trial.
In the event that clinical evidence of a safety event (thrombosis or seizure) occurs or is brought to the investigator or treating physician's attention during the infusion of the IMP, the infusion must be stopped. This will be recorded as part of the trial documentation and safety monitoring.

SAE

An independent Data Monitoring Committee will monitor safety of participants and will report to the Trial Steering Committee. The study may be stopped by the sponsor at any time for safety reasons. The standard Sponsor DMC contract and Charter will be prepared containing details of membership, terms and conditions and full details of stopping guidelines. The DMC will report their recommendation to the independent chair of the TSC.

RANDOMISATION AND BLINDING

Randomisation will be to TXA or placebo in a 1:1 ratio. Due to the emergency situation, a straightforward randomisation process will be used, where sites will simply open the next available lowest numbered treatment pack, which will be a numbered box containing either TXA or placebo according to a computer-defined sequence. Boxes will be identical with the exception of the treatment pack number. Randomisation will be stratified by site with supply to each site balanced for TXA and placebo, using random permuted blocks of varying size. Nottingham Stroke Trials Unit (NSTU) will provide the randomisation list to the IMP manufacturer Sharp Clinical Services UK.

Blinding: Sharp Clinical Services UK will prepare blinded individual treatment packs containing four 5ml glass ampoules of TXA 500mg or sodium chloride 0.9% which will be very similar in appearance. We do not specify the brand of TXA and saline glass ampoules to be used for IMP production in the protocol or IMP-D due to global availability and supply issues that may jeopardise IMP production. With a generic product it is not possible for the blinded glass ampoules to be absolutely identical. However, the blackout labels and heat shrink wrapping ensure the blinded IMP products are very similar in appearance meaning the risk of unblinding is very low. Furthermore, in the unlikely event that the person administering the IMP is unblinded, we believe the potential for this to negatively impact the integrity of the trial, either by influencing the primary outcome (death at day 7) or leading to allocation bias is negligible.
Allocation concealment: Participants, their families, research staff conducting the enrolment and prescribing treatment, the clinical team looking after the participant and research staff conducting the follow-up will be blinded to the treatment allocation for the duration of the study. The TMG and research staff at the coordinating centre will remain blind to treatment allocation until the data collection is complete, statistical analysis plan (SAP) finalised, and the database is locked. The DMC will have access to data split by treatment group, but will not be informed of group allocation, unless this is specifically requested. The TSC will remain blinded, unless a concern requiring unbinding is raised by the DMC. The TMG and the study statistician will only have access to data

relating to the whole cohort. Reports split by intervention (as required by the DMC) will be prepared by an independent statistician in the Nottingham Clinical Trials Unit who will not have contact with participants.

Maintenance of randomisation codes and procedures for breaking code

Clinicians, patients and outcome assessors (clinical, radiological assessors) will be blinded to treatment allocation.
In general there should be no need to unblind the allocated treatment. If some contraindication to TXA develops after randomisation (e.g. clinical evidence of thrombosis), the trial treatment should simply be stopped. Unblinding should be done only in those rare cases when the doctor believes that clinical management depends importantly upon knowledge of whether the patient received TXA or placebo. In those few cases when urgent unblinding is considered necessary, the emergency telephone number should be telephoned, giving the name of the doctor authorising unblinding and the treatment pack number. The caller will then be told whether the patient received TXA or placebo. The rate of unblinding will be monitored and audited. The emergency contact details will be given to the investigators at participating sites.

In the event of breaking the treatment code this will normally be recorded as part of managing a SAE (see below for more details) and such actions will be reported in a timely manner. The Chief Investigator (delegated the sponsor's responsibilities) shall be informed immediately (within 24 hours) of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

TRIAL MANAGEMENT

The trial coordinating centre will be based in the Stroke Trials Unit at the University of Nottingham. The trial will be managed by the chief investigator and the trial management group.
The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

The sponsor will be University of Nottingham and the trial will be coordinated by Nottingham Stroke Trials Unit (NSTU) in conjunction with Nottingham Clinical Trials Unit (NCTU). This will include trial management, data management, database development, provision of the randomisation list to the IMP manufacturer and maintenance and statistical analyses and reporting. The Trial Management Group (TMG) will be responsible for the day-to-day management of the trial. The TMG will be responsible for ensuring project milestones are achieved, meeting at least monthly throughout the duration of the trial.

The trial will consist of a UK base with UK participating sites and an international element involving a number of international sites. Separate local approvals will be sought for the international sites, all applicable local regulations will be adhered to, and a contract will be in place between the University of Nottingham and those sites apportioning liabilities and responsibilities for the conduct of the study.

A Trial Steering Committee (TSC) will be established to include an independent chair, two independent members and a patient representative in accordance with Sponsor and NIHR HTA

guidance. The TSC will provide trial oversight, monitor trial progress and conduct and will act, when appropriate, on the recommendations of the Data Monitoring Committee (DMC). The TMG will report to the TSC. The TSC and DMC will meet before the trial commences to approve the protocol, then 6-monthly in the first instance and then at least yearly at their discretion.

An independent Data Monitoring Committee (DMC) will be established to include an independent chair, disease specific expert and statistician and will be privy to data as the trial progresses, with a remit of assessing safety events (including but not limited to seizures, thrombo-embolism, arterial occlusive events and death, SARS and SUSARs) and efficacy outcomes during trial recruitment. The Chair of the DMC will communicate with the Independent Chair of the TSC.
A DMC charter will be drawn up in line with the DAMOCLES Study Group guidance.("A proposed charter for clinical trial data monitoring committees: helping them to do their job well," 2005) The DMC Charter will define the schedule and format of DMC meetings, the method and timing of interim reports and stopping rules. The stopping rules are based upon a combination of presence of 'proof beyond a reasonable doubt' and the likelihood that the results would change clinical practice. They are not purely mathematical stopping rules, but are strongly influenced by the Peto rule(Peto et al., 1977) where a difference would generally need to be of the magnitude of at least three standard errors. The frequency of such analyses will be determined by the DMC and does not need to be pre-specified, but the minimum frequency will be recorded in the charter. Any decision for premature disclosure of unblinded results to the TSC by the DMC would be justified on the basis of an appropriate combination of mathematical stopping rules and scientific judgment.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Participant Duration

The maximum duration of each participant's involvement in the study will be 6 months.

Study Duration

Study duration will be 7 year 4 months.

End of the Trial

The end of the study will be database lock following completion of the last 6-month follow-up of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment setting

Participants will be recruited from emergency departments, acute stroke services/units across the UK and worldwide. UK participants will be recruited from NIHR Clinical Research Network sites who have dedicated staff to facilitate recruitment and follow-up.
The study will be co-adopted by the NIHR Clinical Research Network Stroke and Injuries & Emergencies portfolios in the UK to enable efficient recruitment from the emergency department. Inclusion of sites outside the UK will both boost recruitment and enhance the external validity of the trial. While the majority of participants will be from the UK, it would not be possible to deliver a definitive study of this size without international enrolment. International sites will allow the question be answered more efficiently, increasing access to potentially eligible subjects, allowing us to reach the recruitment target quicker and provide better value for money.(Minisman et al., 2012) We have selected international sites that are comparable to those in the UK, with similar clinical pathways and models of care for ICH patients.

Care pathway: This pragmatic study is designed to match the clinical care pathway for acute stroke with rapid brain imaging to assess suitability for hyper acute treatments with a 4.5-hour time window such as thrombolysis. Patients will be assessed for eligibility immediately after the CT scan confirms diagnosis of ICH. The emergency consent procedure will facilitate enrolment out of hours and simple randomisation will enable the IMP to be given rapidly in the scanner (IMP treatment should be started within the 4.5 hours inclusion window), as with thrombolysis for ischaemic stroke. Enrolment into TICH-3 will be in addition to standard care, which includes lowering high blood pressure as recommended in clinical guidelines.(Hemphill et al., 2015; National Institute for Health and Care Excellence, 2019) This is important as blood pressure lowering was the significant interaction in TICH-2, and a synergistic relationship between blood pressure lowering and TXA is biologically plausible.

Equality diversity and inclusion for study participants: Historically women and patients from Black, Asian and minority ethnic (BAME) communities have been underrepresented in stroke trials. Our pragmatic inclusion criteria and emergency consent process, which does not require the availability of partner or relative to consent to enrolment should increase inclusivity. Furthermore, in keeping with the NHS Long Term Plan around health inequality in research we embed a SWAT aimed at reducing inequalities in enrolling participants from minority communities. See later in protocol for details of SWAT.

Participants will be recruited from emergency departments, acute stroke services/units across the UK and worldwide. The initial approach will be from a member of the patient's usual care team (which may include the investigator). Due to the emergency nature of ICH we will use an ethically approved emergency consent process to allow enrolment of patients without the capacity to consent for themselves. We have worked closely with our stroke survivor group to develop the consent approach.

If needed, the usual hospital interpreter and translator services (as used in clinical practice) will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not routinely be available printed in other languages. In Wales, information sheets and consent forms will be available in Welsh.

It will be explained to the potential participant (or their relatives if patient lacks capacity) that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. See below for further details regarding withdrawal.

Eligibility criteria

Inclusion criteria:

Adults (≥ 18years) within 4.5 h of onset of acute spontaneous ICH (confirmed on brain imaging). When onset of symptoms is unknown patient must be within 4.5 hours of symptom discovery and have no other exclusion criteria.

Exclusion Criteria:

i. Patient with a known indication for TXA treatment (e.g. traumatic brain injury).
ii. Patient with contraindication to TXA
iii. Patient known to be taking therapeutic anticoagulation with warfarin or low molecular weighted heparin at time of enrolment. Patients taking direct oral anticoagulants can be included and are not excluded.

iv. Massive ICH for which haemostatic treatment seems futile (This would ordinarily be when haematoma volume is estimated as larger than 60ml)
v. Severe coma (Glasgow Coma Scale <5)
vi. Decision already taken for palliative (end of life) care with withdrawal of active treatment

Justification for inclusion/exclusion criteria:

Haematoma volume (HV): HV is one of the strongest predictors of haematoma growth and is independently associated with outcome after ICH. Previous work from us and others have suggested that patients with baseline HV >60 mls (+/-10%) are destined to have a poor outcome (as assessed by a mRS of >3) and hence are to be excluded from TICH-3.
Measurement of HV can be done simply using the ABC/2 method(Kothari et al., 1996) in less than a few minutes. Whilst this measurement is pre-dominantly a research tool, it is increasingly used in clinical practice. If ABC/2 measurement is not possible in the time available a simple single measurement of the largest haematoma diameter provides an accurate estimate, if the length measurement is greater than 5cm the haematoma volume is likely to be greater than 60mls and the patient should be excluded(Bath et al., 2019).

Time: The risk of haematoma expansion is related to time from symptom onset, with risk of haematoma expansion being the highest in the first few hours and plateauing by 6 hours. Whilst other TXA studies have shown greatest efficacy when given within 3 hours of bleeding, these were in patients who did not have brain imaging available to target patient selection. IMP treatment should be started within the 4.5 hours inclusion window. By measuring HV on brain imaging we are able to exclude those who have already undergone significant expansion and least likely to benefit. We will include only those with HV < 60 mls (+/-10%) who the investigators believe still have the potential to benefit from haemostatic therapy. Furthermore, 4.5 hours is the time window for thrombolysis in ischaemic stroke allowing us to mirror the clinical pathway for ischaemic and haemorrhagic stroke, making use of recent developments for rapid imaging and diagnosis in patients presenting within 4.5 hours of stroke onset.
Patients in whom time of symptom onset is unknown (such as wake up stroke) may be included provided that the CT scan does not show HV>60mls (+/-10%) and as long as the patient is presenting within 4.5 hours of wake-up or discovery as they may have the potential to benefit from haemostatic therapy as they have not already undergone catastrophic haematoma expansion (as confirmed by HV < 60 mls).
Patients who are potential neurosurgical candidates will not be excluded from TICH-3 as the decision on whether a patient is a candidate for neurosurgery can take some time – and we do not want to encourage investigators to delay enrolment.
Patients with intra-ventricular haemorrhage (IVH) will not be excluded as they contribute approx. one third of patients with ICH. IVH volume is not routinely measured in clinical practice, and we believe any attempt to ask investigators to measure IVH volume will be unsuccessful and delay enrolment and treatment.

Anticoagulation: Patients taking direct oral anticoagulants may be included as there is equipoise amongst clinicians around whether TXA is beneficial after ICH. The recently concluded TICH NOAC confirmed that it is possible to randomise these patients to TXA or placebo.

Pregnancy: We have not excluded participants who are of childbearing age or who are pregnant as this is an emergency study and it is not possible to delay enrolment to check for pregnancy.

Furthermore, the single dose is rapidly excreted and has an established safety profile, being utilised in pregnant women for the treatment of post-partum haemorrhage (Peitsidis & Kadir, 2011). IV TXA used off-label has been tested in randomised trials (WOMAN, CRASH, etc) for the

treatment (WOMAN Trial Collaborators, 2017) (Ducloy-Bouthors 2011; WOMAN Trial Collaborators 2017) and prophylaxis of postpartum haemorrhage in females prior to vaginal or caesarean delivery (Novikova 2015; Saccone 2019; Sentilhes 2018; Simonazzi 2016; Xia 2020). Additionally, according to the FDA, only animal studies have assessed TXA in early pregnancy with results showing no evidence TXA causes impaired fertility or harm to the foetus (Food & Drug Administration, 2013).

Pregnancy Risk Assessment: ICH is a medical emergency with the potential for rapid deterioration and the majority of ICH patients will be seen and treated in emergency departments. It is not practical or possible to perform a pregnancy test in patients of child-bearing age before they are enrolled. The time delay to intervention would create a time window during which haematoma expansion could occur, haematoma expansion is the commonest cause of death after ICH. The risk of haematoma expansion is likely to greatly outweigh the risk of TXA in the first trimester of pregnancy. However, the final decision of eligibility is whether the treating physician/clinician's 'uncertainty' as to whether or not to use TXA in a particular patient with ICH.

Breastfeeding: TXA has been shown to be safe amongst women who are breastfeeding (Ahmadzia et al., 2021) both at the time of delivery as well as a follow up study 1-3 years post TXA administration which showed no adverse effects were reported to both mother and infant (Gilad et al., 2014). In TICH-3 breastfeeding will be stopped for a minimum of 3 days.

Expected duration of participant participation

Study participants will be participating in the study for a maximum of 6 months.

Removal of participants from therapy or assessments

Withdrawal

Participation in the trial is voluntary. Participants are free to withdraw from the trial at any time without giving a reason. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

The participant will be asked if they wish to withdraw from any or all; of follow-up with participant contact, or follow-up without participant contact. Unless the participant withdraws from follow-up, this will be continued as per protocol even if they have withdrawn from treatment. If the participant declines continued personal participation but allows data collection from other sources (such as the general practitioner and hospital databases) follow-up data will be collected via this route. If the participant is temporarily withdrawn from trial medication by a member of the clinical team, they may restart the trial treatment within the original timescale. Withdrawal, and the reasons for withdrawal, if given, will be documented in the CRF.

Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Participant removal from the trial due to adverse events: In any participant who experiences an adverse event the trial medication may be withdrawn permanently or temporarily halted at the discretion of the clinical team. Should the participant not receive the complete intervention, they will remain in the trial and be followed up until the end of the trial, as completeness of follow-up is essential.

Loss to follow-up

Every effort will be made to trace participants lost to follow-up. Hospital databases, records from the general practitioner and details of third persons given by the participant will be checked to determine whether the participant is alive, what his/her health status is, and whether there are any new contact details. Participants will only be defined as lost to follow-up once phone calls, texts messages and letters to the participant and next of kin have not been responded to.

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator.

Informed consent

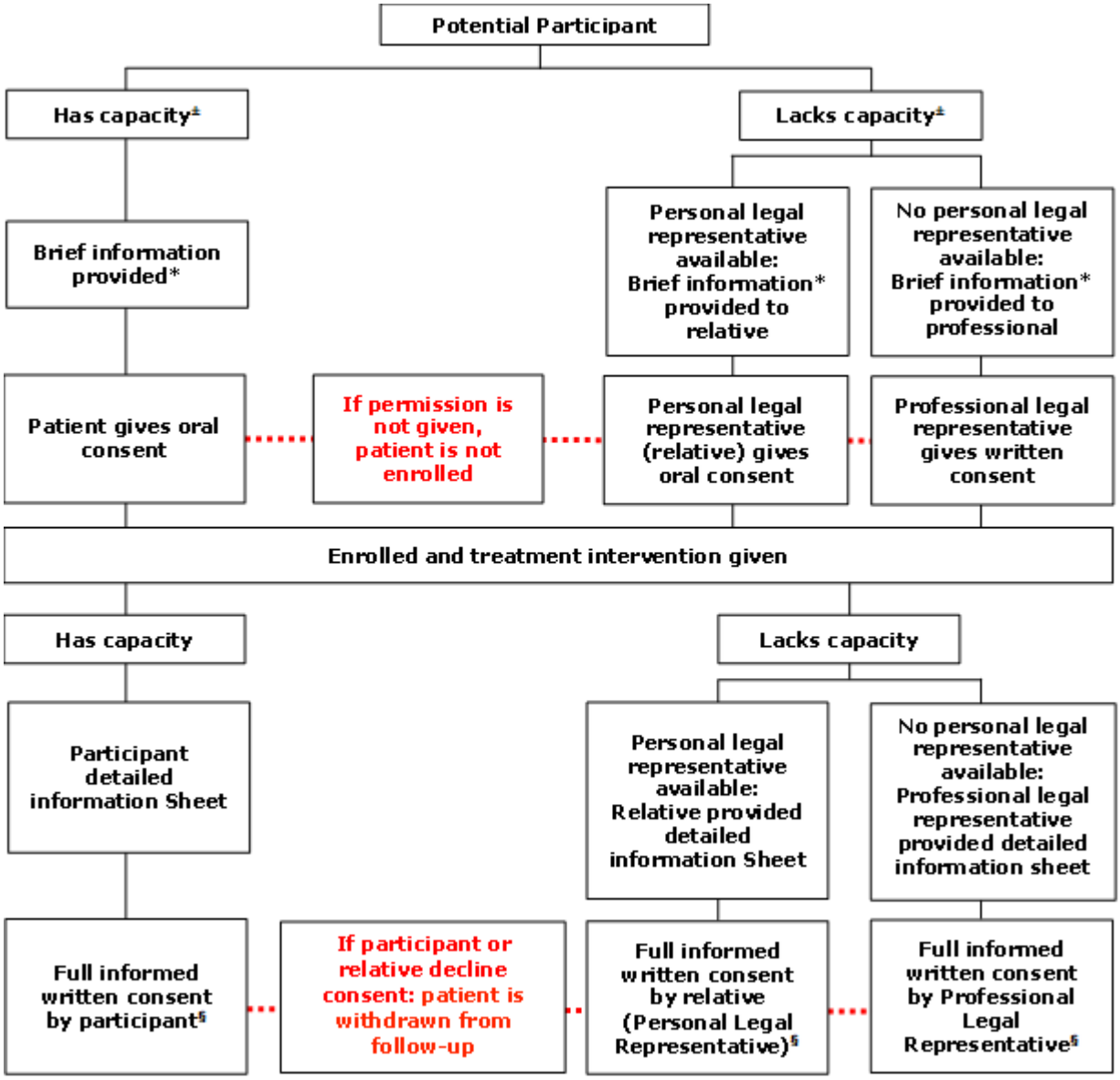
ICH is an emergency condition, that requires urgent treatment, and there is evidence from trials in traumatic extracranial bleeding that TXA is more effective when given early [25]. The need for urgent treatment in the TICH-3 trial means that the implementation of the research should not be delayed and that it would be inappropriate to delay treatment until fully informed written consent can be obtained, either from a patient, relative or other legal representative.
Therefore, oral consent from the patient themselves or their legal representative will be used in the first instance in order to not delay the treatment and so that the treatment pack can accompany the patient to the CT scan to be administered as soon as possible after confirmation of the ICH. All methods of consent are to be recorded in the participants medical notes.

The following processes are to be followed:

Patient has capacity: The emergency nature of ICH means that time prohibits obtaining full written consent even if the participant has capacity. The participant's attending clinical care team will determine if the patient has capacity to consent. If the attending clinician considers it appropriate, the potential participant will be asked if they are willing to be recruited. Specifically, the responsible doctor or delegate will explain that the patient has had stroke caused by bleeding in the brain known as intracerebral haemorrhage (ICH) and will receive the usual emergency treatments for ICH. That, in addition to the usual care, the patient may be enrolled in a research study that aims to improve the treatment of patients with ICH once confirmed by a brain scan. It will be explained that the study is being done to see whether using a drug called TXA will help patients with ICH by reducing the amount of bleeding into the brain, therefore preventing further brain damage. If enrolled in the study the patient will be given an infusion into a vein of either TXA or a dummy medicine (a liquid which does not contain TXA, called a placebo). The doctor or appropriately trained healthcare professional, will explain that TXA has been shown to improve outcome in patients with other types of severe injury and bleeding and that TXA appeared to be safe. However, whilst we hope that TXA will improve recovery after ICH, at present we cannot be sure about this. A brief information sheet will be provided but detailed written information will only be provided if the patient requests at this point. If time allows, written consent will be obtained. If not, verbal consent will be obtained followed by written consent.
If requested, the detailed information sheet will be provided. If they say yes, the potential participant will be randomised **using this initial oral consent**. The case report form and medical records will record that initial oral consent was given. Full, written informed consent will be sought as soon as practicable, ideally within the next 24 hours. Written informed consent will be sought for access to medical notes and for participation in the trial follow up. The participant information sheet will be provided to the participant at this time if not already provided. This approach has been successfully in other hyperacute stroke studies.

Time: Potential participants will be given as long as they need to consider whether they wish to go ahead with study treatment, however we recommend that a maximum of approximately 10 minutes should be taken obtaining initial oral permission (consent). It will be explained to the potential

participant that as this is an emergency treatment, with a small potential therapeutic time window. If the potential participant does not want to decide in such a short time frame they will not be enrolled.



±Assessment of capacity is the responsibility of the treating clinical team
*Further written information provided if requested or required and questions answered. Independent doctor will sign at this stage
§If the patient dies before written consent can be obtained, the participant data collected to date is utilised – to exclude this data would introduce bias in the trial
$If the patient does not regain capacity and has no relatives, the participant data is utilised – to exclude this data would introduce bias in the trial

Patient lacks capacity to give consent

The participant's attending clinical care team will determine lack of capacity. If the potential participant lacks capacity to give meaningful consent (e.g. in cases of dysphasia, confusion, or reduced conscious level) the following procedure will be employed:

Legal representative present: If a legal representative (relative, personal legal representative or other person suitable to act as a legal representative and able to represent the patient's presumed views and wishes) is present or can be contacted rapidly by telephone in the time frame required, bearing in mind the emergency nature of the clinical situation, they will be provided with brief information about the trial.
Specifically, the responsible doctor or delegate will explain that the patient has had a stroke suspected to be caused by bleeding in the brain known as intracerebral haemorrhage (ICH) and will receive the usual emergency treatments for the stroke. In addition to the usual care, if ICH is confirmed then the patient may be enrolled in a research study that aims to improve the treatment of patients with ICH. It will be explained that the study is being done to see whether using a drug called TXA will help patients with ICH by reducing the amount of bleeding into the brain, therefore preventing further brain damage. If enrolled in the study the patient will be given an infusion into a vein of either TXA or a dummy medicine (a liquid which does not contain TXA, called a placebo). The doctor or appropriately trained healthcare professional will explain that TXA has been shown to improve outcome in patients with other types of severe injury and bleeding and that TXA appeared to be safe. However, whilst we hope that TXA will improve recovery after ICH, at present we cannot be sure about this. A brief information sheet will be provided if practicable and time allows but further detailed written information will only be provided on request at this point. If the legal representative objects to the inclusion of the patient in the trial, their views will be respected, and the patient not enrolled

If no relatives (or other representative able to represent the patient's presumed views and wishes) are immediately available the clinical team can seek the opinion of an independent doctor who is prepared to act as the legal representative and sign a consent form.

For participants who were enrolled following agreement by an independent doctor, as soon as relatives are contacted or when the patient regains capacity, a detailed information sheet will be provided, and written consent sought for continuation in the trial.

In event of a patient dying after being enrolled by a professional legal representative but before relatives can be contacted for consent the clinical team should inform the relatives of the patient's involvement in the study and provide information about the study as appropriate, either using approved written information or verbally as per the relatives wishes.

During the process of recruitment and randomisation, the type of consent taken will be documented and monitored to ensure all those with initial oral consent are followed up with written consent, where possible.

Where obtaining this written confirmation of fully informed consent if it is not possible for practical reasons despite all reasonable attempts, such as when the patient does not regain capacity, or if no relatives are available, the patient will remain in the trial unless they (or a relative/legal representative acting on the patient's behalf in the event of lack of capacity) subsequently express a wish to withdraw from the trial. Participants or their legal representative will be informed that they are free to withdraw from the trial at any time without giving a reason and made aware that this will not affect their future care. The participants' decision to withdraw would overrule the decision of the legal representative.

Telemedicine: Where the independent doctor assesses the patient via telemedicine, verbal consent will be obtained and witnessed by someone present in the hospital and this will be recorded in the

medical notes. If the independent doctor does not wish to decide via telemedicine the patient will not be enrolled.
If the patient has capacity to consent but is unable to sign because of impairments (e.g. dominant hand weakness), where possible a mark will be made by the participant, verbal consent obtained, witnessed and signed by an independent observer.
If is not possible for the legal representative to provide consent in person, witnessed consent will be obtained via the telephone or videoconference with a witness or using on-line consent forms. This is particularly important if access to hospital for relatives is restricted due to Covid-19 or other emergencies.
The approved eligibility checklist can be used by the clinician (medic) on site or remotely to facilitate out of hours recruitment. This checklist can then be stored in the participants medical notes to confirm eligibility and enrolment into the trial. Full written consent would then be obtained as soon as practicable by a member of the local research team who is GCP trained and delegated the responsibility.
One copy of the consent form will be kept by the participant/legal representative, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.
Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form which will be signed by the participant.

TRIAL / STUDY TREATMENT AND REGIMEN

Table 1 below shows a schematic diagram of screening, procedures and stages, randomisation, trial treatments, baseline & intermediate visits, final visit, and long-term follow-up.

Study Treatment

Trial treatment is administered as intravenous TXA 2g through a venous cannula with a 1g loading dose infusion (10ml in 100ml sodium chloride 0.9% infusion bag) over 10 minutes followed by 1g infusion (10ml in 250ml sodium chloride 0.9% infusion bag) over 8 hours. Placebo treatment replaces TXA with sodium chloride 0.9%.

Justification of dose: A 2g dose will produce plasma concentrations sufficient to inhibit fibrinolysis. In the emergency situation a fixed dose is more practical, the fixed dose chosen is both efficacious and safe for large patients and small patients.
In TICH-2 95% of participants received both the bolus and infusion dose, 5% did not receive the infusion dose. Risk of seizures has been demonstrated with TXA use in cardiac surgery where high doses of TXA are used (up to 9g); TXA doses exceeding 80mg/kg were associated with seizures, and risk of seizures were higher with infusion than bolus.(Sharma et al., 2014) The proposed TICH-3 dose 2g will generate concentrations of 17mg to 50mg/kg assuming weight range of 40-120kg, above the range 10-15mg/l needed to inhibit fibrinolysis well below the 100mg/kg associated with increased seizure risk.
The dose regime chosen was utilised in CRASH-2, CRASH-3, WOMAN and TICH-2 (approximately 55,000 patients) and was safe and well tolerated with no increase in SAE's, VTE or seizures.
Whilst there is the potential risk of accumulation in patients with renal impairment, as TXA is eliminated through renal excretion, the dosing regimen in this trial is a single dose, such that accumulation is expected to be minimal. Hence, dose adjustment is not required in patients with renal impairment. Only a very small proportion of TXA is metabolized by the liver, thus there is no need for dose adjustment in those with liver impairment.

Assessments

Local investigators will collect and enter data over the internet. Data collection is to be kept to a minimum but includes ethnicity, pre-morbid dependency, premorbid clinical frailty score (CFS) (Rockwood et al., 2005) medical history (hypertension, prior stroke, prior Myocardial Infarction, prior Venous Thrombotic Event) and language spoken. Data will be collected within the first 24 hours but does not need to be done prior to randomisation in order to allow rapid enrolment and treatment.

Table 1. Summary of data collection at which timepoint

Assessments	Screening	Baseline Data	Day 7	Death/Discharge	Day 180
Clinical Assessment	x[$]		x		
Eligibility screening	x				
Consent	x				
Randomisation		x			
Administer IMP		x			
NIHSS		x[$]	x[$]		
GCS	x[$]		x[$]		
Blood pressure		x[$]	x[$]		
Anticoagulation and anticoagulation reversal use		x[$]	x[$]		
Safety outcomes		x	x	x	
Clinical Frailty Score (CFS)		x			
mRS		pre-stroke status			x
EuroQoL (EQ5d 5L)		pre-stroke status			x
EuroQoL (VAS)					x
Cognition (AD-8)					x
Resource use			x	x	x
Patient Self report Health Resource Use Questionnaire					x
Fatigue Severity Score (FSS-7)					x

mRS modified Rankin scale; NIHSS National institute of Health Stroke Score; GCS Glasgow Coma Scale, Safety outcomes: including SAEs: serious adverse events; [$]Routine clinical assessment.
Safety outcomes: seizures, thrombo-embolism, arterial occlusive events and death within hospital.

Data collection at follow-up

Following consent, participants will be assessed by the clinical team for baseline characteristics, and on day 1, day 7 and at discharge from hospital. Follow up at day 180 will be via a postal questionnaire or telephone interview as is standard practice in clinical stroke trials. Local investigators will collect and enter data and images via the secure internet link 7 days after randomisation: (or at death if sooner) length of stay, disposition.

The National Coordinating Centre will collect information (blinded to treatment allocation) on primary and secondary outcomes at day 180 (end of follow-up) by postal questionnaire (or by telephone if necessary).

Health economic data: We will prospectively collect data on participants' pre-morbid function (mRS) and HRQoL (EQ-5D 5L and VAS), where possible from the participant if not a relative/friend. Subsequent health care use whilst an in-patient: antihypertensive therapy, do not attempt resuscitation orders (DNAR), admission to intensive care unit, neurosurgical intervention, hospital length of stay, discharge disposition. At day 180 we will collect data on readmissions, institutionalization, days at home and HRQoL (EQ-5D 5L), health and social use using brief patient data proforma (see later for details of health economic outcomes.

Neuroimaging: As part of standard care for acute stroke, all participants will have had a pre-recruitment cranial CT or MRI scan on admission to hospital (prior to enrolment) to confirm the presence of ICH. CT is standard in most UK hospitals. Pre-recruitment CT scans will be collected after recruitment into the trial is confirmed (encrypted data via internet or post) to allow accurate and consistent imaging phenotyping, particularly in respect of HV. Estimation of haematoma size (ABC/2 rule or A< 5cm) will be performed by investigators at sites prior to enrolment. We will not routinely perform follow-up imaging due to the high cost and burden on sites involved. However, where performed for clinical reasons, we will collect cranial CT scans for analysis of imaging outcomes such as change in haematoma volume, perihaematomal oedema and intracranial mass effect.

Follow Up

Performed centrally with postal (or telephone) follow up at day 180.
Postal questionnaires are used widely in clinical trials and measurement of mRS via this method is valid and reliable. In previous studies we have used telephone questionnaires as they allow assessment of cognition and other outcomes, however they are more time consuming and costly. Furthermore, stroke survivors told us they find communication by post less intrusive than phone calls. Hence, we plan to use a postal questionnaire but in participants where this is not returned will confirm participant status and then attempt to contact participants by phone and complete the questionnaire over the phone. The questionnaire can be completed by the participant or a proxy. This approach was successfully used in 8000 participants with stroke in the HTA funded study, SO2S (Roffe et al., 2017).

There are increasing calls to measure cognition after stroke and ICH, as patients are at increased risk of dementia. The measurement of cognition through an informant is validated, and the Washington University Dementia Screening Tool AD-8(Galvin et al., 2007) is a self-rating tool that can be used by patient or informant, hence making it suitable as an affordable tool in this large pragmatic study. AD-8 has been validated in a number of languages.(James E. Galvin & Zweig)

Concomitant and Rescue Medications and Treatments

Enrolment into TICH-3 will be in addition to standard care, which includes lowering high blood pressure as recommended in clinical guidelines.(Hemphill et al., 2015; National Institute for Health and Care Excellence, 2019) Antihypertensive treatment will be given according to clinical need at the discretion of the treating clinician, in accordance with clinical guidelines. We will record BP and use of acute BP lowering treatment as part of the case report form. For patients taking DOAC at time of enrolment, standard of care may include reversal of anticoagulation in accordance to clinical guidelines. We will record use of anticoagulant and reversal treatment as part of the case report form.

Accountability for drugs & placebos

Each site will maintain an accountability log and be responsible for the storage and issue of study medication. Following a brain scan that confirms ICH, consent and randomisation, treatment will be prescribed. The research team will record administration of the drug to the patient on the participant's CRF. Unused and partially used supplies will be returned to pharmacy. This will be recorded in the pharmacy study log.

Management of study drug overdose

No specific antidotes are available. The study drug will be administered by slow intravenous injection by qualified nursing staff so the potential for overdose is not anticipated.

Urgent Safety Measures

TXA has been used extensively and has an established safety profile.
Urgent safety measures will be taken as necessary to protect a research participant when that participant is identified as being at risk of harm in relation to their involvement in the study.

Urgent safety measures will be communicated to the MHRA immediately. The sponsor or their delegate will phone the MHRA Clinical Trial Unit and discuss the event with a safety scientist. The sponsor will then follow-up with notification in writing within three days of the action being taken.

Protocol Deviations and Violations

A protocol deviation is defined as a move away from described procedures. A minor deviation is defined as an action or event that does not affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects.
Minor protocol deviations will not be recorded in TICH-3 in view of the large volume of data relating to the use of TXA in haemorrhage.

Protocol Violation

A protocol violation is a major variation in practice from the trial protocol, for example where a participant is enrolled in spite of not fulfilling all the inclusion and exclusion criteria (e.g. lack of consent, randomisation after 4.5 hours after ICH), or where deviations from the protocol could affect participant safety, the trial delivery or interpretation significantly.

All protocol violations must be reported to the Chief Investigator, via the online electronic case report form and/or telephone call. The CI will notify the Sponsor if a violation has an impact on participant safety or integrity of the trial data. The Sponsor will advise on appropriate measures to address the occurrence, which may include reporting of a serious GCP breach, internal audit of the trial and seeking counsel of the trial committees.

Criteria for terminating trial

The trial may be terminated by either the TSC, the sponsor or the funders if there is overwhelming evidence of major safety concerns, new information, or issues with trial conduct (e.g. poor recruitment, loss of resources). The trial may be stopped at individual centres due to unacceptable performance in recruitment and/or failure to comply with protocol.

Any unused and partially used drug and placebo shall be returned to the local pharmacy.

RADIATION EXPOSURE

Details of diagnostic or therapeutic ionising radiation

A pre-recruitment CT head scan is performed at the time of presentation with acute stroke as routine clinical care, whether or not the patient goes on to participate in the trial. This is not considered to be a research-related exposure, although information from the scan is subsequently used to establish eligibility (i.e. by confirming acute ICH).

Patients who are enrolled into the trial may subsequently undergo further CT head scans based on clinical need (for example if there is a clinical deterioration) or based on local clinical practice. These scans are considered to be standard of care (SoC). There will be no additional radiation exposure due to the study.

Trial Procedures

Single run non-contrast CT head scan performed as SoC.
There will be no additional radiation exposure due to the study.

TRANSPORT AND STORAGE OF TISSUES

Not applicable – no tissues are to be collected or used in this study.

LABORATORY ANALYSES

Not applicable – no laboratory analyses are used in this study

STATISTICS

STATISTICS

Methods

Statistical analysis will be performed by the trial statistician or their delegate(s) using validated statistical analysis software such as Stata or SAS. All variables will be summarised using descriptive statistics appropriate to their distribution.

The analysis and presentation of the trial results will be in accordance with the CONSORT guidelines and a full Statistical Analysis Plan (SAP) will be developed prior to database lock. The primary objective of the trial is to determine the effectiveness of TXA versus placebo and as such, the principal approach to the primary comparative analysis will be to analyse as randomised without imputation of missing data, with due emphasis being placed on the confidence intervals for the between arm comparisons. Sensitivity and secondary analyses will be considered supportive to the primary. Similarly, analyses of secondary outcomes, will be considered supportive to the results of the analysis of the primary outcome.

Interim analyses of the primary outcome will be performed for review by the DMC only. The frequency of such analyses will be determined by the DMC and will not be pre-specified. They will use this, and other evidence provided in confidential reports presenting data by treatment group, prepared by a statistician independent from the trial, to determine whether the trial should continue. Recommendations to stop, in addition to safety concerns, will be based upon a combination of presence of ‘proof beyond a reasonable doubt’ and the likelihood that the results would change clinical practice. Such a decision would not be purely mathematical but will be strongly influenced by the Peto rule(Peto et al., 1977) where a difference would generally need

to be of the magnitude of at least three standard errors. Examples of where consideration would be given to the trial stopping include, but are not limited to, the following:

- Analysis of death favours the control (hazard) with P<0.02 (2-sided)
- Analysis of death favours the active (benefit) with P<0.001 (2-sided).
- Shift analysis of mRS favours the active (benefit) with P<0.001 (2-sided). The significance level of P<0.001 amounts to 'proof beyond reasonable doubt'.
- Shift analysis of mRS favours the control (hazard) with P<0.02 (2-sided)

Sample size and justification

The null hypothesis is that TXA does not alter death by day 7 in participants with acute ICH. Assuming 10.31% of participants in the placebo group die by day 7 (the proportion observed in TICH-2 participants who would be eligible for TICH-3) 2688 participants per group would allow detection of a difference of 2.57% in the proportion of deaths between the placebo and TXA groups (i.e.7.74% deaths on TXA, OR of 0.73), at the 5% significance level 2-sided with 90% power. This difference is considered by patients and their relatives to be important, clinicians feel that it would change clinical practice, and is plausible, as demonstrated in the sub-group analysis of TICH-2 and the CRASH-II trial. As the primary outcome is death it is anticipated that there will be minimal loss to follow up; in TICH-2 (Sprigg et al., 2018) none of 2325 participants were lost to follow up by 7 days, and in CRASH-3("Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial," 2019) <1% of 12737 participants were lost to follow up. It is therefore planned to include a total of at least 5500 participants with at least 2750 in each treatment arm.

Literature has investigated the reduction in sample size which can be gained by including co-variates in the model for different outcomes: 20% for ordinal analysis of mRS (Peto et al., 1977), between 15% and 44% for survival data(Minisman et al., 2012) and from 3-46 % for dichotomous outcomes (National Institute for Health and Care Excellence, 2019) have been suggested.

Given the uncertainty around the magnitude of a co-variate adjustment to the sample size, a formal reduction will not be made. However, the table below shows the detectable differences with a final sample size of 2688 participants per arm where a co-variate adjustment has been made. All calculations assume a control rate of 10.31%, 90% power and 5% significance level 2-sided. It can be seen that although the required sample size was determined based on an OR 0.73, when covariate adjustment is applied, and sample size is maintained at 2688/arm for analysis, it may be possible to detect a smaller effect. For example, a 20% reduction in sample size due to covariate adjustment would allow detection of an effect size of OR 0.757.

Reduction in required sample size resulting from co-variate adjustment	% deaths in control group	% deaths in TXA group	Detectable effect when sample size maintained at 2688/arm	
			Risk Difference	Odds Ratio
None	10.31%	7.74%	2.57%	**0.73**
5%	10.31%	7.80%	2.51%	0.736
10%	10.31%	7.87%	2.44%	0.743
15%	10.31%	7.93%	2.38%	0.749
20%	10.31%	8%	2.31%	0.757
25%	10.31%	8.07%	2.24%	0.764
30%	10.31%	8.14%	2.17%	0.771
35%	10.31%	8.21%	2.10%	0.778

40%	10.31%	8.30%	2.01	0.787

Sample size calculations were performed using PASS software.

Baseline characteristics
Characteristics of randomised participants will be compared between the two trial arms at baseline, using appropriate descriptive statistics.

Assessment of efficacy

Primary outcome: Early death up to and including day 7 after ICH onset.
The evaluation of the primary outcome will be performed using regression models for binary outcomes, with adjustment for key prognostic factors. The model will be fully specified in the SAP. Absolute and relative measures of effect and 95% confidence intervals will be presented. The primary outcome will also be investigated in pre-specified subgroups using appropriate interaction terms. The subgroups will be specified in the SAP and will, at a minimum include age, sex, systolic blood pressure, HV, GCS, the start of treatment (≤2, ≤3, >3 hours), antiplatelet (yes no), direct oral anticoagulation (yes, no) and intraventricular haemorrhage (yes, no). The trial is powered to detect overall differences between groups rather than interactions of this kind, therefore the analyses will be regarded as exploratory.

Secondary outcomes
Pre-specified secondary outcome of importance: functional outcome: Dependency assessed by modified Rankin Scale(mRS) (Peto et al., 1977) at 180 days using a postal questionnaire (or telephone if postal not possible).

Additional secondary outcomes:
Death up to and including Day 2 after ICH onset.
Quality of Life (EQ-5D-5L) baseline and at Day 180,
Cognition (AD-8) at Day 180.
Fatigue severity scare (FSS-7)

Secondary outcomes will be analysed using appropriate (depending on outcome type and distribution) regression models adjusting for predefined key prognostic factors. Regression models will be used for binary outcomes such as death at Day 2. Dependency at Day 180 measured using the mRS will be analysed using ordinal logistic regression adjusting for key prognostic factors. The results of these analyses will be considered supportive to the primary.

Assessment of safety

The following safety events will be recorded in the first 7 days (or death if sooner):
1) venous thromboembolism
2) arterial occlusive events
3) seizures
Fatal events occurring before discharge will also be collected.
These will be summarised using appropriate descriptive statistics according to the treatment the participant received irrespective of randomisation. Where a participant did not receive any intervention, they will be summarised separately. Where a participant did not receive a full dose of the intervention, they will be summarised as though they had.

AEs and SAEs that do not meet the criteria for safety events will not be collected in keeping with the MHRA's proportional approach to clinical trials of investigational medicinal products.

TXA has an established safety record in 50,000 non-surgical patients(Devlin et al., 2018) and was safe in TICH-2 where patients randomised to TXA had less SAEs at day 2, 7 and 90. Given the participants are in the acute stage of an ICH, there will be a significant number of SAEs and AEs that are related to the stroke but not TXA. We believe that collecting large numbers of unrelated SAEs will adversely increase burden on sites and the trial team without increasing safety for participants. Focus is therefore on events that are highly likely to be related to the study medication. In view of this we will not collect all SAEs – however we will collect data on pre-specified safety outcomes (seizures, thrombo-embolism, arterial occlusive events and death (the primary outcome)) occurring within the first 7 days. This design is in-keeping with the MHRA's proportional approach to clinical trials of investigational medicinal products, as we believe TXA represents a low-risk intervention. This approach has been taken by other investigators.

Procedures for missing, unused and spurious data

It is expected that missing primary outcome data will be minimal, and the primary analysis will use all available data i.e. missing data will not be imputed.
Analysis of secondary outcomes will also not use any methods of imputation for missing data.
All efforts will be made to obtain missing data and to query spurious data.
Further information will be included in the SAP.

Definition of populations analysed

Intention-to-treat dataset: All randomised participants
Per protocol dataset: All participants in the intention-to-treat population who are deemed to have no major protocol violations that could interfere with the objectives of the study. The per-protocol population will be defined in a blinded review prior to database lock
Safety dataset: All randomised participants.

The primary and secondary outcomes will be analysed according to the Intention to Treat principle using all available data from randomised participants and analysing according to treatment allocation, irrespective of treatment received (the intention to treat dataset) Sensitivity analyses of the primary and key secondary outcomes will be performed using the per protocol dataset.
Safety data will be summarised using the safety dataset, according to the treatment the participant received irrespective of randomisation. Where a participant did not receive any intervention, they will be summarised separately. Where a participant did not receive a full dose of the intervention, they will be summarised as though they had.

Further details will be provided in the SAP.

Feasibility assessment (Stop-go Decision)

Decision to proceed to main phase – The recommendation to proceed from the internal pilot phase to the main phase of the trial will be made by the TSC approximately 18 months after recruitment start. It will be based on safety (as assessed by the DMC) and information about recruitment. The recommendation will be provided to HTA for ratification.

It is assumed that non-UK sites should have been recruiting for 6 to 12 months when the stop-go decision takes place.

Table shows the decision matrix to be used for the recommendation to proceed.

	Red	Amber	Green
% Threshold	<50%	>50-99%	100%
Recruitment	<500	500 -999	1000*
Active sites	<43	43-84	85*
Rate/site/month	<0.35	0.35-0.64	0.65
Action	Discuss trial viability with TSC and HTA	Continue – action needed: protocol TSC meeting, protocol review, assess & resolve barriers, assess feasibility of increased recruitment at active sites, review site selection, increase site numbers	Continue

Note: As a minimum requirement 65% of the active sites (55 sites) and 65% of the participants (650) will need to be UK-based in order to meet the green criteria.

It is important to note there will be no break in recruitment unless the stopping criteria are met.

HEALTH ECONOMICS

The primary health economics analysis will take an NHS and personal social services cost perspective, in accordance with NICE guidance. Secondary analysis will take wider societal perspective to capture the broader effects of TXA versus Usual care including out of pocket expenses and potential effect on carers and families. This will enable a broader societal perspective to be reported alongside a health service perspective.

Cost

Health resource data will be collected from a hospital perspective from first admission to discharge this will include Length of Stay (LOS); ICU stay; neurosurgical intervention; antihypertensive therapy and Do Not Attempt to Resuscitate orders (DNARs).

A purposely designed self-reported Health Resource Use Questionnaire will be used to capture participant-level resource information for health care use at day 180 for the previous 3 months. Whilst we know this is not ideal, we have the intense period for cost comparison whilst a hospital inpatient. We do not want to ask the patient to record longer than 3 months at day 180, as patient memory is poor beyond this point and asking for a longer recall imposes a greater patient burden. Two intense cost collection periods enable health economic analysis to be performed on TXA versus usual care base between the groups based on initial inpatient stay and day 90 to 180 costs. The 180-day questionnaire will collect data on all aspects of participant treatment and follow-up including inpatient and readmissions and outpatient hospital visits, medication, rehabilitation and primary and community care use over the last 3 months. The questionnaire will be designed with input from the trial patient advisory group and seek to capture all relevant resource drivers yet minimise burden on the participants. The Health Resource Use Questionnaire (to be submitted to the UK health economists DiRUM database) will ensure the key resource implications for TXA versus control are captured. This resource data will then form the units on which cost data, using sources such as the Unit Cost of Health and Social Care, Personal Social Services Research Unit (PSSRU) of the British National Formulary (BNF), and national reference costs can be attached.

Outcome

The main outcome measures for the economic evaluation will be the QALY (EQ5D-5l) at day 180 and discharge.

Secondary measures will include time at home (or usual residence) at day 180

Discharge destination post I/P stay

Analysis

A number of health economic analysis will be performed.

1. Interim cost effectiveness analysis from a health and social care perspective at discharge.
2. Cost effectiveness analysis of TXA versus usual care at day 180 from a societal perspective based on days at home / discharge destination.
3. Cost utility analysis of TXA versus usual care at day 180 from a societal perspective.

An incremental analysis will be used between the two trial arms. The net monetary benefit framework will be used to estimate the extent to which, and the probability that, TXA is cost effective option compared to usual care. An Incremental Cost Effectiveness Ratio (ICER) will be calculated, if appropriate, in the 12 months from randomisation. Cost Effectiveness Acceptability Curves (CEACs) showing the probability of effectiveness versus willingness to pay at the NICE threshold of £20,000-£30,000 per QALY will be constructed. Key cost drivers will be examined using probabilistic sensitivity analysis.

ADVERSE EVENTS

Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.
An AE does include a / an:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

Known side effects of TXA: Gastrointestinal disorders (nausea, vomiting, diarrhoea) may occur but disappear when the dosage is reduced. Hypotension has occasionally been reported after rapid intravenous infusion. Rare instances of colour vision disturbances have been reported following long-term use. Rare cases of thromboembolic events have been reported. Rare cases of allergic skin reactions have also been reported.

TXA will counteract the thrombolytic effect of fibrinolytic preparations, but these would be contra-indicated in patients with haemorrhagic stroke.

Reference safety information: Section 4.8 of the SmPC for TXA, date of last revision 11 April 2019, will act as the reference safety information.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. disease or disorder being studied, or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the IMP or placebo that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be assessed for seriousness, expectedness and causality by local investigator.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse reactions and SUSARs

Participants will be asked to contact the study site immediately in the event of any serious adverse reaction (SAR) or SUSAR. All SAR, SUSAR and all pre-specified safety events (venous thromboembolism arterial occlusive events, seizures and deaths) will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator (delegated responsibility by the Sponsor) shall be informed immediately (within 24 hours) of any serious adverse reactions and shall determine seriousness and causality in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant or the partner of a trial participant monitoring shall not occur during the pregnancy and after delivery due to the short half-life of TXA and its frequent use in obstetrics.

All SAR, SUSAR and pre-specified safety events (venous thromboembolism arterial occlusive events, seizures and deaths) will be recorded and reported to the MHRA and REC as part of the annual Development Safety Update Reports. SUSARs will be reported within the statutory timeframes to the MHRA, and REC as stated below. The Sponsor shall ultimately be responsible for adverse event reporting. AEs and SAEs that do not meet the criteria for safety events will not be collected in keeping with the MHRA's proportional approach to clinical trials of investigational medicinal products.

Urgent Safety Measures

An Urgent Safety Measure is a procedure taken to protect a research participant when that participant is identified as being at risk of harm in relation to their involvement in a research project and urgent action, which deviates from the approved protocol, is required to manage the event and protect the participant.
Any urgent safety measure relating to a Clinical Trial of an Investigational Medicinal Product (CTIMP) should be communicated to the MHRA immediately. They advise that sponsors phone the MHRA Clinical Trial Unit and discuss the event with a safety scientist. The sponsor must then follow-up with notification in writing within three days of the action being taken. The notification should be in the form of a substantial amendment and should describe the event, the measures taken and justification for the measures taken.

SUSARs – see appendix 1

A serious adverse event that is either sudden in its onset (anaphylaxis), unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the

IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- If the event is deemed a SUSAR, shall, within seven days, enter the required data on the MHRA's eSUSAR web site.
- Shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

TRIAL TREATMENT RELATED SAES

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment but not the IMP shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed related to the trial treatment shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
- Shall, within a further eight days send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

Participant removal from the study due to adverse events

Any participant who experiences a serious adverse reaction may be withdrawn from the study at the discretion of the Investigator. Clinical need and participant safety will be the priority. However, as the treatment is given in first 8 hours only it is likely that the intervention will have been completed – and withdrawal from follow up may not be appropriate. The participant (or legal representative) retains the right to withdraw at any time without giving a reason.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible, and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced but reflect the emergency situation and time critical nature of the intervention.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a trial identity code number (country number, centre number and randomisation number), allocated at randomisation, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available). The date of birth (dd/mm/yyyy) is

entered into the database once for the use of data verification and is not visible when entering study data.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in case additional follow-up is required. CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (MHRA).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. Paper CRFs (such as the returned day 180 follow up forms) will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Electronic CRFs will be stored on a secure dedicated web server. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).
Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log will be stored on-line (secure dedicated web server) in addition to record of training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; drug accountability, pharmacy records.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

In the context of the COVID-19 pandemic, visits to hospital sites are generally not appropriate and in the context of this trial they generally would not influence the reliability of the trial results or the well-being of the participants. In exceptional circumstances, NSTU may arrange monitoring visits to sites as considered appropriate based on perceived training needs and the results of central statistical monitoring of study data. The purpose of such visits will be to ensure that the study is being conducted in accordance with the protocol, to help site staff to resolve any local problems, and to provide extra training focused on specific needs. Therefore, no routine source data verification will take place.

Where corrections are required, these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice

from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Simultaneous oral presentation at a large international stroke conference, publication in high impact journal will ensure maximum impact and rapid dissemination with incorporation into guidelines. Stroke survivors and carers will inform dissemination to patients and public which is likely to include social media and a roadshow.
Participants will not be identified in any publications.

USER AND PUBLIC INVOLVEMENT

This trial builds on work with stroke survivors and their carers in previous studies (TICH-1 and TICH-2), with particular focus on emergency consent methods and choice of outcome measures. We will continue to work with stroke survivors and their carers throughout the trial. In addition, we are committed to increasing inclusivity and representation in our trial and have invited a member of the Leicester BAME PPI group to join the TSC.

The Nottingham Stroke Research Partnership Group have been involved in the co-design of the consent methods for many years now. The group, comprising of stroke survivors and their families, feel is not acceptable that patients miss out on the opportunity to participate in clinical trials because their ICH stroke occurs out of working hours e.g. overnight when the research team is not around. The trial has been co-designed in a pragmatic manner to support enrolment out of hours, in a risk proportionate approach. The PPI group strongly support emergency consent methods that enable patients with ICH to be offered participation into the TICH-3 based on an approved eligibility checklist and information about the trial.

Results will be presented to stroke survivors and the public at multiple forums, including the Stroke Assembly lay conference in the UK and across Europe using the Stroke Alliance For Europe (SAFE) network.

Dissemination plan will be developed with the PPI group. Likely to involve a results 'Roadshow' of meetings to lay members around the UK.

Web-hosted lay summary in text and video format developed with the stroke survivor group and Black, Asian and Minority ethnicity Applied Research Collaboration group. Use of social media, Twitter, news broadcasters (with a press release as for TICH-2 and CRASH-3).

STUDY FINANCES

Funding source

This Trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (NIHR129917). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Study Within a Trial (SWAT):

Currently members of BAME communities are under-represented in research in general and specifically in research in Stroke.(Devlin et al., 2018) In trials in emergency settings, this is often seen in differential deferred consent and follow up return rates. A great deal of effort is often expended in recruiting participants to trials. Ensuring that as many of these participants as possible are recruited, retained and provide outcome data can greatly improve research efficiency and minimise the risk of bias resulting from incomplete data.

In the TICH-3 trial, we will use emergency consent processes, adapted for the emergency situation. Written consent for continuation and follow up in will be taken once the participant is able to do so. Outcome data is collected at 180 days after randomisation through postal or telephone questionnaires. It is hypothesised that improving communication and understanding of the trial rationale, events to date and the importance of their input and the extent of the commitment involved with people from BAME communities may increase rates of consent to follow up and increase response rates to follow up questionnaires.

Data from TICH-2 trial in a similar participant population using emergency consent procedures, demonstrated a difference in follow up return rate at 3 months of people from BAME communities compared to non-BAME communities (96.5% vs 98.7%; p = 0.004).

The SWAT will investigate the effects of an animated video to improve inclusiveness to consent for follow up and retention rates. We will work with colleagues and PPI groups at the centre for BAME health at Leicester University to create an animated video about the trial that will be dubbed into 3 – 4 key languages as well as in English, to be shown to participants (and or their legal representative). The video will be used in addition to the standard consent process and information sheets. Given the age and recent stroke, the intervention may improve understanding of all participants not just those in BAME groups, we will therefore include all UK participants rather than the sub-set from BAME communities in the SWAT.

Population: individuals recruited to the TICH-3 trial in the UK.
Intervention: Animated participant video
Control: standard consent process and information sheets
Outcome measures: 1.Proportion providing consent for follow up i) in the TICH-3 UK study population as a whole and ii) by BAME versus non-BAME 2. Follow up completion rates in the control and intervention groups.

Method of allocation will be cluster randomisation. Using data from the TICH 2 trial, we will match population demographics at UK sites and randomise sites to either the intervention or control.

Analysis: One interim analysis is planned 36 months after the start of the trial. We predict 1100 participants will have been enrolled in the UK, and 850 will have reached the 180 day follow up timepoint. If there was strong evidence of an effect on follow up completion at 180 days of either control or intervention, the strategy showing the greatest return rate would then be implemented for

all future participants. Otherwise the SWAT will continue until the end of the trial. Analyses will include appropriate descriptive statistics and between-group comparisons for each strategy using multivariate regression models.

Dissemination Details will be registered on the Northern Ireland MRC Trials Hub for Methodology Research SWAT registry. Results will be published in a peer review journal. The findings will be made publicly available as soon as possible after the end of the SWAT and will be made available to researchers conducting meta-analysis in this field, including via the Northern Ireland MRC Trials Hub.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)___ Professor Nikola Sprigg_____

Signature:_____

Date: _____

Trial Statistician: (name)__ Trish Hepburn _____

Signature:_____ _____

Date: _____

Trial Pharmacist: (name)____Cherrelle Evans_____

Signature

Date: _____

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Appendix 1: Reference safety information

Section 4.8 of the SmPC for TXA, date of last revision 02 February 2021, will act as the reference safety information.

A serious adverse event that is unexpected in its severity and seriousness is classified as a SUSAR and requires expedited reporting. For example, a seizure that is fatal would be unexpected in terms of severity, whilst pulmonary embolism is often fatal and therefore may not be considered unexpected in severity. Any event suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

EXPECTED EVENTS NOT SUBJECT TO EXPEDITED SUSAR REPORTING			
After tranexamic acid the following events are expected and therefore not subject to expedited SUSAR reporting:			
Gastro-intestinal	**Cardiovascular**	**Central nervous system**	**General**
Abdominal pain	Arterial thrombosis any site	Convulsions	Anaphylaxis
Diarrhoea	Deep vein thrombosis (DVT)	Disturbance in colour vision	Fatigue
Gastrointestinal disturbance	Collapse	Dizziness	Flushing
Nausea	Hypotension	Headache	Hypersensitivity including oropharyngeal swelling, urticaria, angioedema
Vomiting	Ischaemic stroke	Seizure	Musculoskeletal pains
	Peripheral artery embolism		Rash
	Pulmonary embolism (PE)		
	Tachycardia		
	Venous thrombosis any site		